Università degli Studi di Padova

PhD course in Molecular Medicine, XXXI cycle

Curriculum: Regenerative Medicine

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The prognostic role of magnetic resonance imaging in patients with Primary Sclerosing Cholangitis

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ACADEMIC YEAR 2017-2018

CONTENTS

ABBREVIATIONS

PSC, Primary Sclerosing Cholangitis

MRI, Magnetic Resonance Imaging

MRC, Magnetic Resonance Cholangiography

MRCP, Magnetic Resonance Cholangiopancreatography

LT, Liver Transplantation

IBD, Inflammatory Bowel Disease

CRC, Colorectal Cancer

ERCP, Endoscopic Retrograde Cholangiopancreatography

CBD, Common Bile Duct

RHD, Right Hepatic Duct

LHD, Left Hepatic Duct

DS, Dominant Stricture

CCA, Cholangiocarcinoma

ALP, Alkaline Phosphatase

IHBD, Intrahepatic bile ducts

EHBD, Extrahepatic bile ducts

LS, Liver Stiffness

TE, Transient Elastography

DWI, Diffusion-weighted imaging

GBCA, Gadolinium-based Contrast Agents

AST, Aspartate Aminotransferase

ALT, Alanine Aminotransferase

γGT, Gamma-glutamyl Transpeptidase

CD, Cystic Dilatations

DS, Dominant Stenosis

ET, Endoscopic Treatment

CHAPTER 1

Introduction

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease that involves intra- and extrahepatic biliary duct characterized by biliary inflammation, development of biliary strictures and often evolution toward biliary cirrhosis and end-stage liver disease[1]. The disease can vary among patients, indeed different subtypes of the disease have been described. Moreover, the clinical presentation and the evolution over time may strongly differ between patients, also with the same subtype of the disease. No medical therapy has proven to be effective to halt disease progression, and liver transplant is the only therapy able to improve survival in these patients. In the last thirty years many groups of researchers have analysed the prognosis of the disease and performed several prognostic models, based on a variable combination of clinical, biochemical, histological and cholangiographic features of the disease [2]. These models were designed in order to assess the disease severity and to provide physicians with a risk of developing major outcomes and/or the predicted survival. At present, none of these scores is recommended to be used in individual patients [3]. Recently, a new composite score, built in a large population of PSC patients has showed promising results in the prognostication, moreover, as output it gives the 5-, 10- and 15- years survival probability, thus representing a useful tool, easy-to-use in clinical practice [4].

The research in this disease presents some inherent problems, due to the fact that the disease is rare and significantly variable. To overcome these problems, in the last years, scientists made a great effort to build networks among centers with interest and expertise in this and other cholestatic and autoimmune liver diseases, namely the International PSC Study group, the Global PBC study group and the International AIH Study group. Among these, the International PSC Study Group is a group composed by scientists of more than 20 countries,

with the aim to coordinate PSC research projects between leading institutions. Thanks to this large scientific network, for example, an enormous cohort of PSC patients was collected for genetic studies[5] as well as for clinical studies[6]. Moreover, this large collaborative group has contributed to attract the interest of drug companies in this disease and this is confirmed by the increasing number of clinical trials in the last years. Thus, it is crucial to have adequate tools to select patients for clinical trials, and these tools should be able to assess disease subtype, severity and prognosis.

The perfect tool should be: 1) able to assess all the different stages of the disease, included the early stage (only biliary involvement); 2) assessed by non-invasive modality; 3) not expensive; 4) easy-to-use; 5) time-saving; 6) high reproducible in the same patient, in different patients and by different physicians; 7) widely available.

Of course, the perfect tool has not yet been proposed and unfortunately, I won't be able to do that at the end of the book. But, dealing with reality, I am reporting here the results of my research regarding the potential role of magnetic resonance imaging (MRI) in assessing prognosis in patients with PSC.

Magnetic resonance cholangiography (MRC) is recommended as the first diagnostic modality in patients with suspected PSC [3,7] and its potential role in assessing prognosis is justified by its non-invasive nature, its reproducibility and its adequate performance in assessing biliary alterations in PSC that resulted comparable to that of endoscopic cholangiography [8]. The latter, being invasive, is not recommended for patients' follow-up.

Thus, the aim of this thesis was to analyze the prognostic value of radiological findings by magnetic resonance imaging in patients with PSC. With this aim, the research was largely conducted in the French National Reference Centre for Inflammatory Biliary Disease and Autoimmune Hepatitis at Saint Antoine Hospital in Paris, Sorbonne University. This is the

reference center for this disease in France and the radiologists of the center have a relevant expertise in magnetic resonance abdominal imaging and specifically in cholestatic liver disease. Moreover, some projects have involved other centres, including the National Institute for Health Research, Biomedical Research Center in Birmingham and the McGill University Health Center di Montreal other than, obviously, the Centre for Rare and Cholestatic Liver Disease of the University Hospital of Padova. Finally, I contributed to a project held from the Hamburg-Eppendorf University and another project of the Hannover University Medical School about the prognostic role of MRI in PSC and the results have not been included in this thesis.

This thesis is composed by eleven chapters, included this chapter. Chapters from 2 to 4 include a general overview of the disease, a review of known prognostic factors and scores of the disease and then I describe the role of magnetic resonance imaging in PSC. In Chapter 5,

I elucidate the aims of the experimental projects. In Chapter 6, I report data regarding the evaluation of the prognostic value of two magnetic resonance score in PSC. In Chapter 7, I analyze the use in combination of magnetic resonance score and liver stiffness in assessing prognosis. In Chapter 8, I characterize a cohort of PSC patients with intrahepatic bile duct cystic dilatations found at MRI, suggesting that it represents a new variant of classical large duct PSC and I discuss the possible pathogenetic mechanisms involved in the development of cystic dilatations. In Chapter 9, I review the results of published studies regarding the endoscopic treatment of dominant strictures in PSC, underlining the open issues in this field and In Chapter 10, I assess the presence of radiological and clinical predictive criteria of response to endoscopic treatment in these patients. Finally, in Chapter 11, I provide a general conclusion and the possible future directions of the research.

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CHAPTER 2

Primary sclerosing cholangitis

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PRIMARY SCLEROSING CHOLANGITIS: A GENERAL OVERVIEW

PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of intra- and/or extrahepatic bile ducts leading to the formation of multifocal strictures alternated to bile ducts dilatations. The disease is rare but PSC represents a relevant cause of morbidity and mortality since it's often evolutive and it can lead to cirrhosis and its complications. The only effective therapy to extend survival in PSC patients is liver transplantation (LT), since no pharmacotherapy has been proven to be effective to halt disease progression.

The disease is associated to inflammatory bowel disease (IBD) in up to 70-75% of patients, and moreover, PSC is associated to an increased risk of hepatobiliary and colorectal cancer (CRC), particularly in patients with concomitant IBD.

Epidemiology

Incidence and prevalence of PSC varies in different studies and different geographical regions but, in general, PSC is more frequent in males with an average age at diagnosis of 30 - 40 years. Annual incidence and prevalence ranges from 0 to 1.3 per 100.000 person-years and 0 to 16.2 per 100.000 person, respectively [1–11], with the lowest incidence (0 - 0.16/100.000) described in Alaskan natives [1] and in Spanish population [2] and the highest incidence reported in Northern Europe (1.22-1.3/100.000) [7,10]. Similarly, highest prevalence has been reported in North America and Northern Europe [3,4,10,7]. IBD associated to PSC has been reported in 20-76% of patients [12,2–7,11,10,13] with the lowest prevalence described in Singapore [12] and the highest prevalence reported in Sweden [7]. Recently, a large multicentric international study, including 7121 patients with PSC seen in 37 centers in Europe, North America and Australia confirmed a prevalence of IBD in PSC of 70% of the population [14]. Temporal trends of incidence of PSC

were assessed in six studies, and all but one demonstrated increasing incidence rates of the disease over time [2,5–7,11]. An increase in prevalence, but not in incidence of PSC was also recently reported in an UK study [9]. Since clinical presentation at diagnosis has not changed over time [11], an earlier diagnosis of the disease is not the attributable cause for the increasing incidence of PSC.

Aetiology and pathogenesis

PSC is characterized by chronic inflammation of the biliary epithelium, resulting in multi-focal bile duct strictures and chronic cholestasis. Chronic inflammation leads to fibrosis development in biliary tree and in liver parenchyma and its possible evolution to cirrhosis.

The aetiology of PSC is largely unknown but increasing evidences suggest that PSC is a complex disorder with environmental, immunobiological and genetic pathogenetic mechanisms [15–17]. There are currently three main hypotheses regarding the pathogenesis of the disease including the involvement of the gut-liver axis, the toxicity of bile acids and the autoimmunity. These three hypotheses are strictly correlated one to each other, and a summary of these theories is reported below.

The strong clinical association between PSC and IBD has stimulated the research of shared pathogenetic mechanisms between the two diseases. The leakage of bacteria or bacterial components, with immunogenic properties, from the gut lumen to bile ducts and the subsequent bile ducts injury was first proposed, but patients with PSC did not demonstrate an increased intestinal permeability [18]. An alteration of gut-liver T cell axis was also proposed. Observations documented that T cells, primarily activated in the gut, are then recruited in the liver because the two organs share the molecular complex for lymphocyte homing. In PSC patients a combination of hepatic inflammation (increased levels of TNFα) and the activation

of VAP1 (a primary amino oxidase and adhesion molecule) by nutrients or bacteria in the portal blood, determines an aberrant hepatic expression of the adhesion molecule, MADCAM1, and the chemokine, CCL25, with subsequent recruitment of $\alpha 4\beta 7$+ and CCR9+ T cells [15]. Moreover, it was recently reported the presence of T-cells of common clonal origin in paired gut and liver samples of PSC-IBD patients thus indicating that these memory T-cells in the gut and in the liver are able to recognize and react to the same triggers [19]. The third hypothesis regarding the gut involvement in PSC pathogenesis takes into account the possibility that an antigen, derived from colonic content, might drive biliary inflammation. Furthermore, the possible alterations of intestinal microbiota, already documented in inflammatory and metabolic diseases, have been explored. A number of studies analysed intestinal microbiota in PSC patients in comparison with IBD only patients and healthy controls and overall, a reduction of microbial diversity in PSC patients was documented [20,21]. The difference in genus and species that characterized PSC patients is strongly variable among different studies [22–29] and some microbiota alterations were correlated to the severity of the disease thus suggesting its role as biomarker of the disease [25,27,28]. The alteration of intestinal microbiota might be a consequence of alteration in the bile acids composition in a direct and indirect way. Indeed, bile acids are able to inhibit the growth of bacteria sensitive to bile [30], to induce enzymes involved in DNA repair and to alter bacterial proteins in different ways. Moreover, bile acids, by activating the nuclear receptor FXR, control cathelicidin expression that is involved in biliary epithelium defence against microbial invasion. On the other hand, bile acids are regulated by intestinal microbiota through the chemical processes of deconjugation, dehydroxylation, dehydrogenation and epimerization. Moreover, intestinal microbiota regulates BA transport. These evidences suggest that a complex cross talk between bile acids and microbiota might be involved in the pathogenesis of the disease [28].

The toxic bile acids hypothesis includes the alteration of bile acids composition due to cholestasis and the alteration of bicarbonate umbrella on the apical surface of the biliary epithelium and the subsequent toxic effect of apolar bile acid in cholangiocytes [31]. Anion exchanger 2 (AE2), cystic fibrosis transport receptor (CFTR) and the glycocalyx stabilising enzyme fucosyltransferase 2 (FUT2) are the main enzymes that guarantee an alkaline environment in the apical surface of cholangiocytes thus preventing the accumulation and the invasion of toxic apolar protonate bile acids in biliary epithelium. Alterations in these and other transporters (e.g. multi drug resistant protein 3, MDR3) might thus contribute to the pathogenesis of cholestasis. Then, during cholestasis an adaptive response aims to limit the toxic effects of bile acids and it is composed by different mechanisms that involve nuclear receptors (e.g. FXR), the apical bile salt receptor TGR5 and the glycocalyx stabilising enzyme fucosyltransferase 2 (FUT2).

The autoimmune hypothesis is supported by genetic studies that identified more than 20 susceptibility genes for PSC. Most of these genes are localized within the human leukocyte antigen (HLA) complex on chromosome 6, and the non-HLA findings are almost all associated with one or more other immune-mediated or autoimmune condition (e.g. type I diabetes, rheumatoid arthritis) [32,33]. HLA class I and II molecules which present antigens to T cells are likely to be involved similarly to what observed for coeliac disease and other autoimmune disease. Unfortunately, in PSC the antigen has not yet been discovered. An element that is contrary to the autoimmune hypothesis in PSC is the lack of benefit from immunosuppressive therapy.

Clinical presentation and diagnosis

The typical presentation of PSC is that of a man of 30-40 years of age with IBD and alterations of cholestatic liver enzymes in whom MRC demonstrates the presence of alternating strictures and dilatation of intra- and/or extrahepatic bile ducts. The symptoms are no-disease specific and are present in roughly 50% of patients, that may typically complain of abdominal pain, pruritus, fatigue, fever [13]. Symptoms of PSC could strongly impact on quality of life of these patients and thus they need to be recognized and treated. Some useful tools, such as the quantitative scale of evaluation of symptoms [34] and questionnaires to evaluate the impact of symptoms on life's quality [35] has been proposed, and they could be used also to monitor the response to treatment of specific symptoms such as pruritus.

The most frequent type of PSC is the *classic* or *large duct PSC* but there are other subtypes of PSC such as small duct PSC, PSC-AIH variant, PSC with high IgG4. The diagnosis of large duct PSC is based on radiological features and the exclusion of causes of secondary sclerosing cholangitis. MRC is the modality of choice for diagnosis of PSC since it's non-invasive, cost-effective compared with endoscopic retrograde cholangiography (ERC) [36]. MRC has adequate sensitivity and specificity (0.86 and 0.94) [37], thus, for all these reasons, it is recommended by both European and American guidelines as first diagnostic modality in case of suspicion of PSC[38,39]. A detailed overview on the role of magnetic resonance imaging in diagnosis of PSC is provided in the Chapter 4. The alteration of cholestatic liver enzymes is frequently the first index of suspicion of PSC in patients with IBD, but it should be kept in mind that cholestatic liver enzymes should spontaneously fluctuate in patients with PSC and could be also normal [40].

Small duct PSC is a less frequent subtype than the large duct PSC, the former ranging between 3.6% to 16% in different studies [5,11,14,41,42] and it appears to be more frequent in female sex [14]

and in children and young adults [43–45]. Small duct PSC, in the presence of a normal cholangiogram, is defined histologically with typical alterations characterized by degenerative changes of small bile duct and bile ductules, periductal fibrosis, mild, non-suppurative fibrous cholangitis, ductopenia and, when the disease progresses, portal tracts might enlarge due to the development of fibrous piecemeal necrosis [46]. The evolution of small duct to classical large duct PSC has been poorly described and varies between 0% to 22.9% in different studies [47–52].

PSC-AIH variant, formerly known as "overlap PSC-AIH", should be suspected when a patient with PSC has a disproportionally elevated serum transaminases and/or serum IgG levels and the confirmation is based on histological evaluation. When confirmed, PSC-AIH variant needs to be treated with immunosuppressive drugs [53]. The prevalence of PSC-AIH variant has been reported in different studies and collectively ranges from 6.6% to 14% [14,53] with a prevalence of small duct subtype of 27% in a study including 26 patients with PSC-AIH variant [54].

Another variant of the disease is the *PSC with elevated IgG4* serum levels, this entity needs to be differentiated by IgG4-associated sclerosing cholangitis, a different disease mostly associated with autoimmune pancreatitis and characterized by a good response to immunosuppressive therapy. PSC with elevated IgG4 levels has been reported in 9-18% of PSC patients [55,56] and this form of PSC seems to have a more severe clinical phenotype and a shorter transplant-free survival compared with large duct PSC [56].

Finally, the *association between PSC and primary biliary cholangitis* has also been reported in a very few cases [57,58].

Once the PSC diagnosis is established, the *coexistence of IBD* needs to be excluded by usual diagnostic modalities (endoscopy with biopsy, histology and radiologic assessment). This diagnostic approach is commonly able to differentiate the diagnosis of ulcerative colitis (UC), more often associated with PSC, from Crohn's disease (CD)[59]. The IBD in patients with PSC is

typically characterized by the presence of pancolitis with right-sided predominance, rectum sparing and backwash ileitis. More relevant, these patients have an increased risk of developing colorectal cancer compared with IBD-only patients [60–62]. IBD in PSC patients is not only a clinically different disease from simple IBD but it is also genetically distinct from classical IBD phenotypes [63,64]. The diagnosis of IBD more often anticipate the diagnosis of PSC but it can also be concomitant or subsequent to PSC diagnosis [14] and IBD may also occurs after LT for PSC [65]. A Norwegian study including 322 patients with IBD who underwent MRC screening found that 7.4% of patients with IBD had a concomitant large duct PSC, and of them, only 2.2% had a prior diagnosis of PSC [66]. These results have been recently confirmed by a French study including 233 IBD patients with abnormal and normal liver tests and 187 non-IBD patients with abnormal liver test. Screening IBD patients by MRC revealed a prevalence of PSC of 9.9% in the group with abnormal liver tests and of 3.3% in the group of normal liver tests [67]. Taken together, these two studies suggest that a MRC might be considered in patients with IBD, even in those with normal liver tests. Further studies in this field are warranted to provide definitive recommendations.

Natural history

The natural history of PSC differs according to the different subtypes of the disease, moreover, different patients with the same subtype of PSC might evolve differently during follow-up. The natural course of the disease could be characterized by occurrence of acute bacterial cholangitis, development of dominant strictures (DS), cirrhosis and its complications and development of hepatobiliary malignancies (cholangiocarcinoma, gallbladder adenocarcinoma, hepatocellular carcinoma), and colorectal cancer.

Acute bacterial cholangitis frequently occurs in patients with PSC in association or not to a dominant stricture, moreover, ascending cholangitis is a complication of endoscopic intervention. Signs and symptoms of acute cholangitis might be less evident in patients with PSC and so it should be suspected also in the absence of the classical Charcot's triad characterized by jaundice, fever with rigors and right upper abdominal pain. When an acute cholangitis is suspected, MRC is recommended, in order to assess the presence of a bile flow obstruction caused by a dominant stricture and thus, in this case, an endoscopic intervention is mandatory [38,68]. Bile duct bacterial isolates are various, including *Enterobacteriacae*, *Enterococci*, alpha-haemolytic *Streptococci*, *Staphylococci* and also fungi, mainly *Candida*. A study aiming to assess bile duct bacterial isolates in explanted liver of PSC patients, has identified that time from last endoscopic retrograde cholangiopancreatography (ERCP) and antibiotic treatment during ERCP are independent predictors of the variety of bacterial isolates in the bile duct of these patients, but not the presence of dominant strictures [54]. On the other hand, a subsequent study reported the presence of *Enterobacteriacae* in bile samples of 40% of patients with dominant strictures but in none of patients without dominant strictures. Moreover, the enteric germ positivity in bile was associated with a worsening of the disease during follow-up compared with patients with dominant strictures but without enteric germs in bile [69]. Finally, a subsequent study from the same group conducted in larger cohort with an extended follow-up, revealed that *Candida* but not bacterial infection in bile samples of patients with dominant strictures was correlated with a poor prognosis and a shorter transplantation-free survival compared to patients with dominant strictures and sterile bile or *Enterobacteriacae* infection [70]. Current guidelines recommend routine administration of prophylactic antibiotics before ERCP in patients with PSC in order to prevent acute cholangitis [38] and moreover, guidelines recommend the administration of antimicrobial

therapy associated to correction of bile duct obstruction in dominant strictures in order to resolve acute cholangitis [38,71]. Finally, American guidelines recommend that patients with recurrent bacterial cholangitis should be treated by prophylactic long-term antibiotic and evaluated for liver transplant [71], but this indication to LT is not world-wide accepted. No studies have assessed the existence of predisposing factors to develop acute cholangitis during the course of PSC other than the presence of DS.

Dominant strictures. The term dominant defines the presence, at ERCP, of a stricture of common bile duct (CBD) with a diameter of ≤ 1.5 mm and/or a stricture of right (RHD) or left hepatic duct (LHD), within 2 cm of the bifurcation, of ≤ 1.0 mm [72]. This is an arbitrary definition proposed 16 years ago by Stiehl *et al.*, useful to define the severity of strictures found at ERCP. One limitation of this definition is that the measure of the stricture could change according to the filling pressure of contrast during injection, moreover it does not include the clinical significance of the stricture. Dominant stricture (DS) in PSC could be benign, thus representing an evolution of the progressive obliterative fibrosis around the bile duct, or in a minority, but extremely relevant, of cases could be malignant, representing a cholangiocarcinoma (CCA) arisen from a bile duct stricture. The frequency of dominant strictures in PSC patients varies in different studies and ranges between 35.9 and 54.8% [13,40,72,73] of patients and in 5% of patients, DS was associated to cholangiocarcinoma in one study [73]. The presence of DS in PSC patients is not invariably associated to symptoms nor increase in cholestatic enzymes. Actually, presence of symptoms, such as pruritus, fatigue, abdominal pain and acute cholangitis varies widely between different studies [34,72,74–85,73,86–88] with a variable percentage of asymptomatic patients with DS that underwent endoscopic treatment with or without an increase in cholestatic enzymes. The definition of dominant stricture according to the ERCP

features could not be applied to MRI given the spatial resolution of MRI in extrahepatic bile ducts is lower than ERCP (voxel size 1 x 1 x 1 mm) and the lack of hydrostatic pressure during MRI[89,90]. Thus, up to now no MR definition has been identified and validated to describe DS. A consensus by the International PSC study group regarding the definition of DS has not yet been obtained [68], but the general feeling is to change the adjective "dominant" in "significant" including in the latter, the concept of the clinical significance of the strictures. Therefore, the new definition of DS will presumably include both the MRC features and the clinical relevance of the stricture. As a matter of fact, current European guidelines, recommend to perform endoscopic treatment with concomitant ductal sampling (brush cytology, endobiliary biopsies) of suspected significant strictures identified by MRC in PSC patients who present with symptoms likely to improve following endoscopic treatment [38]. Similarly, previous American guidelines recommended to treat DS in patients with pruritus and/or acute cholangitis to relieve symptoms [39]. The quality of evidence of these recommendations is low since there are no data regarding the predictive factors of improvement after endoscopic treatment. Endoscopic treatment of DS could improve symptoms, liver tests, cholangiogram and moreover, it could improve actual survival compared with the estimated survival predicted by the Mayo model [72,82,85]. The type of endoscopic treatment has been recently the topic of an international multicenter randomized trial that demonstrated, in a large cohort of PSC patients, that simple balloon dilatation and short-term stenting are equivalent in term of efficacy but stenting is associated to an increase risk of serious adverse events. Thus, the authors concluded that balloon dilatation is preferable compared to stent as first treatment of dominant stricture in patients with PSC, especially in those with intact papilla [87]. A detailed revision of literature regarding the endoscopic treatment of PSC patients with dominant strictures is present in the Chapter 9.

Cholangiocarcinoma

PSC is a premalignant condition with an increased risk of developing cholangiocarcinoma (CCA), that occurs in 6-13% of patients [13,14,61,73,91–95], with a cumulative frequency during follow-up of 20% [11] and an annual incidence of 0.6-1.5% [92,93,95]. CCA is diagnosed during the first year after the diagnosis of PSC in up to 50% of patients [11,14,91,92,95]. The risk of hepatobiliary malignancies in PSC patients is increased of 160-fold compared with the general population [92], and an increased risk of developing hepatobiliary malignancies was observed in PSC patients with large duct subtype *vs.* small duct and PSC-AIH variant, in patients with PSC and ulcerative colitis *vs.* Crohn's disease and finally, in males *vs.* females [14]. CCA in PSC arise is 76% at hilum but it could appear also as an intrahepatic mass lesion and a distal bile duct stricture. The clinical presentation of CCA differs according to its localization and stage, being the early stage mostly asymptomatic [95], on the other hand symptoms such as abdominal pain and weight loss associated to a rapid deterioration of liver function with jaundice suggest the possibility of advanced CCA or a benign dominant strictures. The first diagnostic approach in case of suspicion of CCA is based on a combination of various techniques, including ERCP associated to brush cytology (and endobiliary biopsies) and various imaging modalities including MRC. Bile duct brushing for diagnosing CCA is highly specific (97%) but its low sensitivity (43%) limits its utility for surveillance of CCA in PSC [96]. Fluorescence in situ hybridization (FISH) or equivalent chromosomal assessments should be considered in patients with suspected CCA when brush cytology results are equivocal; similarly additional investigation such as cholangioscopy, endoscopic ultrasound, and probe-based confocal laser endomicroscopy (pCLE) may be used in selected cases [38]. Serum carbohydrate antigen (CA 19-9) has a poor diagnostic performance whether used alone or in combination with one diagnostic modalities due to a low sensitivity and specificity and its diagnostic performance

increases when it is used in association with cross-sectional imaging performed during the follow-up of these patients [95]. The International PSC study group recommends the use of MRI/MRCP with contrast media before an ERCP or percutaneous cholangiogram if there is a concern for CCA and in general within 6 months from the diagnosis of PSC due to the risk of CCA within the first year of diagnosis [68].

The utility and modality of surveillance of CCA is an open issue and no recommendations regarding the surveillance of intra-or extrahepatic CCA are provided neither by American or European guidelines, except for the annual ultrasound recommended for surveillance of gallbladder polyps. Thus, different centers worldwide have a different approach to this issue, ranging from the regular endoscopic surveillance performed at Helsinki University Hospital [97] to annual imaging (with ultrasound, CT scan or MRC) plus CA19-9, or either no surveillance, in case of refused surveillance, as recently described in a study conducted at the Mayo Clinic [98]. The results of the former type of surveillance are not yet available, differently, the study from Ali, Tabibian *et al.*, despite the number of methodological issues, suggests that hepatobiliary carcinoma surveillance improves outcomes, including survival, in these patients [98]. The International PSC Study Group in a recent position statement underlined that many experts in the field of PSC recommend regular CCA screening with MRI/MRCP [68].

Gallbladder involvement

Gallbladder abnormalities have been observed in 41% of PSC patients [99,100], and they are represented by the presence of gallstones in one fourth of patients, wall thickening independent by the presence of portal hypertension in 15% of patients and mass lesions in 4-6% of patients. In PSC patients mass lesions in the form of polyps are malignant in 56-57% of cases [99,101], thus justifying the annual surveillance by ultrasound in these patients [39,71,102].

Moreover, the discover of gallbladder polyps constitutes *per se* an indication to cholecystectomy according to both European and American (AALSD) guidelines [71,102] independently from the size of the polyp. Differently, American Gastroenterological Association (AGA) guidelines, recommended cholecystectomy in polyp greater than 8 mm [39]. Finally, an increase of the pre- and post-prandial gallbladder volume compared with healthy controls was described in PSC patients [103,104] but the reason for this increased volume and its eventual clinical relevance has not yet been elucidated.

Colorectal Cancer (CRC). Patients with PSC have a 5-fold increase risk for CRC compare to general population, 95% of CRC occur in patients with PSC-IBD. Patients with PSC and UC have a higher risk of developing CRC compared with age- and sex-matched general population (9-fold increase) and compare with UC controls (10-fold increase)[11]. The crude incidence rate of CRC in PSC is 4.8 per 1000 person-years [9]. Moreover, CRC occurs at a younger age in PSC-IBD patients compared to IBD controls and the mortality for CRC is as high as 50% in patients not undergoing a regular endoscopic surveillance compared to 16% in patients in regular surveillance [11].Thus, in patients with PSC and IBD current guidelines recommend to perform yearly surveillance with ileocolonoscopy with dye-based chromoendoscopy with targeted biopsies [38].

Cirrhosis and its complication

The natural course of patients with PSC often includes the progression of biliary fibrosis to cirrhosis and the development of its common complications. No medical treatment has demonstrated to be effective to halt disease progression and to improve survival. Ursodeoxycholic acid, despite the lack of consistent evidences to recommend in favour or against its prescription at low dose (13-15 mg/Kg/die), it is diffusely prescribed since it

demonstrated its ability to improve biochemical cholestasis and surrogate markers of prognosis in these patients. Different other pharmacological approaches have been studied but, up to know, no clear effectiveness in term of improvement of survival have been proven for any of these approaches. Different clinical trials with new drugs are now ongoing. Liver transplantation is the only therapeutic option that improves survival in patients with PSC. Besides the classical indications to liver transplant, common to other liver diseases, there are some indications that are PSC specific even if not worldwide recognized. A poor quality of life due to the presence of severe pruritus, resistant to medical therapy, and/or the presence of recurrent cholangitis despite antibiotic prophylaxis is the indication to liver transplant in up to 43% of patients with PSC in Norway [105]. Moreover, the presence of suspected biliary neoplasia confirmed by two subsequent bile duct brushing positive for dysplasia is an indication both in Norway and in Finland [97,105] and very selected cases of hilar cholangiocarcinoma are transplanted in the US. There are a number of specific issues of post-transplant management in PSC patients but their discussion goes beyond the aim of this overview.

Survival

The results of studies aiming to analyse transplant-free survival in patients with PSC strongly differ depending on whether the data have collected in transplant and non-transplant centers. Actually, median survival ranges between 9.6 - 13.2 years in the transplant and between 18 - 21.3 years in the non-transplant setting [11,13,41,106]. Weissmuller *et al.* analysing 7121 PSC patients reported a transplant free survival of 14.5 years, that reflects the presence of a high number of specialized and transplant centers within the International PSC Study Group.

Overall survival of patients with PSC is significantly reduced compared with general population, with a 3-fold increased risk of death compared with age- and sex- matched healthy

population [9]. Death occurs in 12-18.4% of patients with PSC [8,11,41,106] with a relevant percentage of PSC-related death. CCA-related death has been reported in up to half of cases followed by cirrhosis complications and/or liver failure, liver transplant complications and CRC [11,41,106].

The survival of patients with PSC is different according to the subtype of disease. Indeed, patients with small duct PSC have a significantly longer transplant-free survival compared with patients with large ducts PSC [11,14,47–51] and CCA rarely occurs in these patients [11,14,47,49–52], unless the disease has progressed to large-duct PSC [48]. Differently, patients with PSC-AIH variant appear to have a transplant-free survival comparable to patients with large duct PSC [11,14] but the risk of hepatobiliary malignancies in PSC-AIH variant seems to be reduced compared to the large duct form [14,107]. In one study the survival of patients with DS appeared to be lower than the survival of patients without DS but this data could be influenced by the high percentage of death due to development of CCA in the former group in contrast with the absence of CCA in the latter [86]. Patients with ulcerative colitis and PSC showed a lower survival compared with patients with Crohn's disease or without IBD [14].

Finally, survival may differ also within the same subtype of the disease and the study of the possible prognostic factors of this disease has been one of the topic of the research during the last 30 years and an overview of biomarkers and clinical scores predicting prognosis in PSC will be provided in the Chapter 3.

CHAPTER 3

Prognostic indices in primary sclerosing cholangitis

Nora Cazzagon

PROGNOSTIC INDICES IN PRIMARY SCLEROSING CHOLANGITIS

The variability of the natural course of the disease and the absence of an effective drug therapy to halt disease progression has stimulated the research of prognostic factors possibly associated to clinical outcomes of this disease. Several prognostic factors have been proposed, including biochemical, cholangiographic, histological, elastographic factors and their combination in composite prognostic scores. Moreover, in the last years the increasing collaboration between different groups has allowed to collect relevant number of cases of this rare disease thus providing more and more robust data regarding the natural history [14] and prognosis [43,108].

Biochemical findings

Alkaline phosphatase (ALP) is a clinical measure of cholestasis and several observational studies, using different criteria, have demonstrated that ALP is significantly associated to prognosis in PSC patients. Stanich *et al.* showed, in a retrospective cohort, that the occurrence of at least one ALP reduction under the upper normal limit, during 10 years follow-up, was associated with a lower occurrence of clinical endpoints (CCA, LT and death from all cause), and a better survival compared to patients with persistent abnormal ALP [109]. Moreover, taking advantage of prospective data from the high-dose UDCA trial, they confirmed that ALP normalization was associated to a better prognosis [109]. The main limits of this study were the retrospective design and the *post-hoc* analysis of the UDCA trial. A similar study including 139 PSC patients followed-up in Oxford reported that a persistent reduction of ALP < 1.5 ULN was associated with a lower frequency of clinical end points, here defined as cirrhotic

decompensation, liver transplant and liver-related deaths including deaths for CCA, and a longer end point-free survival compared with patients who did not achieve persistent ALP reduction. Moreover, they reported a similar frequency of endpoints in patients with complete ALP normalization and in patients with ALP reduction < 1.5 ULN [110]. The *post hoc* analysis conducted in the Scandinavian UDCA trial [111] demonstrated that PSC patients with a reduction of ALP of at least 40% or a complete normalization after 1 year, had a higher endpoint-free survival regardless of UDCA therapy compared with the group of patients who did not achieve the improvement. In this study, the longest survival was reported in the group of patients treated with placebo and having ALP reduction. These and previous results, despite the obvious statistical issues, suggest that ALP reduction *per se* is associated to a better outcome in PSC patients regardless the UDCA use. Rupp e*t al.*, examined data of a large prospective database including 281 PSC patients under UDCA treatment, followed up in Heidelberg, where a yearly follow-up with ERCP in patients with dominant strictures is in place. They defined two different criteria of ALP reduction according to the follow-up interval. The first criteria combined the reduction of ALP of at least 50% from baseline, the reduction to less than 1.5 the ULN or ALP normalization after 6 months; the second criteria was ALP reduction below 1.5 time of ULN within 12 months. They also assessed the all previously reported criteria of ALP reduction. Their results showed that both criteria were independently associated to transplant-free survival, and they also confirmed the prognostic value of ALP normalization or its reduction below 1.5 times the ULN. Finally, de Vries *et al.* analysed in 366 PSC patients included in a Dutch multicentric retrospective database, the association of ALP with outcomes (LT and PSC-related death). A positive association between levels of ALP at diagnosis, at 1 year after the diagnosis and the hazard of reaching an endpoint were reported. The optimal prognostic threshold for ALP was 1.3 times the ULN, 1 year after the diagnosis.

Harrell's C-statistics for ALP in predicting clinical endpoint in this study was 0.65 (95% CI 0.55-0.68) [112]. Thanks to its prognostic value, ALP has been incorporated in 3 over 11 proposed composite prognostic scores [108,113,114].

Bilirubin

Bilirubin has been incorporated in 8 of the 9 PSC specific prognostic score [13,49,108,113–118] and in end stage liver disease score [119,120]. Since in PSC patients, bilirubin value is susceptible of transient elevations during episodes of acute bacterial cholangitis or in presence of DS of bile duct, Tischendorf *et al.* evaluated the prognostic value of persistent elevation of bilirubin. They observed that patients with a persistent elevation (> 3 months) had a poor prognosis with an estimated median survival of 30 months [13].

Albumin and INR

Low albumin and an elevated INR are signs of advanced, decompensated liver disease and they are poorly sensitive in early phase of disease. Albumin has been incorporated in five PSC specific and non-specific prognostic scores [13,108,115,116,120]. On the contrary, INR has been incorporated only in Child-Pugh score and MELD score.

ELF test

The enhanced liver fibrosis (ELF®) test is a marker of fibrosis composed by three circulating markers of hepatic matrix metabolism: hyaluronic acid, tissue inhibitor of metallopropteinases-1 and propetide of type III procollagen. In a first study, ELF test was proven to be able to predict LT-free survival independently of the Mayo risk score both in a derivation and validation panel composed by 167 and 138 PSC patients, respectively. The

reported area under the receiver operating characteristics curve (AUC) of ELF test in discriminating patients with or without an endpoint (liver transplant or death) was 0.81 (95% CI 0.73-0.87). Moreover, the combination of Mayo score and ELF seemed to be able to improve classification [121]. An external multicentric retrospective validation including 534 PSC patients subsequently confirmed these results [122].

Interleukin (IL)-8

Serum IL-8 was found to provide excellent discrimination for LT-free survival in two cohorts of independent PSC patients and, by multivariate analysis, IL-8 resulted associated to LT-free survival independently from age and disease duration. Anyway, when comparing the prognostic value of IL-8 to ELF® test and the Mayo risk score, the latter two were stronger predictors of transplant-free survival [123].

Biliary calprotectin

In the same study, calprotectin in bile, obtained during ERCP, resulted the protein alone that had best ability to distinguish between mild and advanced PSC, classified according Amsterdam cholangiographic criteria. The prognostic value of biliary calprotectin has not yet completely elucidated [123].

IgG4

The presence of high serum level of IgG4 in up to 9% of PSC patients was associated to a more severe disease and prognosis in these patients as confirmed by significantly higher total bilirubin, ALP, Mayo risk score and a shorter time to liver transplantation despite similar biliary and pancreatic involvement compared with PSC and normal IgG4 serum levels [55]. The

prognostic value of elevated IgG4 serum levels in PSC patients has not been reproduced in further studies.

VAP-1

Vascular adhesion protein (VAP)-1 is an adhesion molecule endowed with potent amine oxidase activity expressed that is increased, in its soluble form, in patients with PSC and it has been found to be an independent predictor of cirrhosis and poor LT-free survival in these patients [124].

Anti-GP2

The pancreatic autoantibody, anti-glycoprotein 2 (anti-GP2) positivity was found in about 50% of patients of a Norwegian and German cohorts composed respectively by 138 and 180 PSC patients. The anti-GP2 IgA positivity was correlated to marker of disease severity, it was strongly associated to CCA and to a shorter LT-free survival in both cohorts, at least in part explained by an increased frequency of biliary tract cancer. Indeed, in Cox regression analysis Mayo risk score but not anti-GP2 was independently associated to LT-free survival [125].

Morphological features assessed by ERCP and MRI

Intrahepatic disease

Two studies conducted in the nineties examined the existence of a correlation between the cholangiographic findings evaluated by ERCP and prognosis [126,127]. In the first study, Craig *et al.* revaluated retrospectively the first available cholangiogram of 129 patients followed up at the Mayo Clinic, and they correlated cholangiographic findings with the occurrence of hard

endpoints (death or liver-transplant). They analysed intrahepatic and extrahepatic portions of the biliary tree separately and they described strictures by evaluating grade, length and extent of the strictures. They recorded the highest grade and the greatest length of strictures according to the interpretation model proposed by the same group in 1983 [128]. Moreover, they separately categorized the extent of involvement of intrahepatic bile ducts (IHBD) and extrahepatic bile ducts (EHBD) as either localized or diffuse, and recorded the presence and degree of bile duct dilatation for IHBD and EHBD.

They reported a significant impact on LT-free survival of patients with high grade IHBD strictures and a diffuse involvement of IHBD but they did not observe a significant impact on survival of the grade, length and extent of EHBD strictures. Moreover, they observed a trend toward a significant difference in survival between patients according to the presence of severe IHBD dilatation. Finally, the high-grade of IHBD and EHBD strictures and IHBD dilatation were associated with the presence of cirrhosis. A multivariate analysis to evaluate independent predictive factors of liver transplant-free survival was not performed [126]. A few years after, Olsson and Asztély confirmed in a Swedish cohort of 94 patients that high-grade intrahepatic strictures were associated with the early onset of jaundice and shorter survival and they suggests that the grade of intrahepatic strictures should be incorporated into survival models of PSC [127].

Amsterdam Score

In 2002 Ponsioen and colleagues described the natural history of a large multicentric cohort composed by 174 Dutch patients with PSC and they evaluated the prognostic value of the cholangiographic findings. Indeed, all the earliest available cholangiographies were reviewed and analysed according to a modified version of their cholangiographic classification [129]. This

system combined qualitative, rather than quantitative, criteria of severity of intra- and extrahepatic bile duct involvement. Then, having assumed that both intra- and extrahepatic bile duct changes would have reflected the disease severity, they combined IHBD, EHBD findings and age at ERCP (all three significant at Cox regression model) to build the Amsterdam score. They then demonstrate that the score was able to distinguish between different risk categories, associated to different median survival [106]. The main limits of this study, besides the invasive nature of the method, are the lack of data regarding the inter-observer and intra-observer variability of cholangiographic interpretation and the arbitrary assumption that a combination of IHBD and EHBD findings would have impact on prognosis of these patients despite previous observations have reported the prognostic value of intrahepatic and not extrahepatic findings [126,127]. The model was then modified and validated in an external cohort of Norwegian patients and confirmed an adequate performance [130].

Arterial peribiliary hyperenhancement

Two studies reported on the analysis of the prognostic values of magnetic resonance imaging and magnetic resonance cholangiography features in PSC patients [131,132]. Petrovic *et al.* reviewed the first available MRI/MRCP of 49 PSC patients in order to evaluate the existence of a correlation between MRI findings and the revised Mayo prognostic risk score calculated at the time of MRI. In this study, bile duct anomalies were classified according to the criteria adopted by Ponsioen to derive the Amsterdam cholangiographic score and the degree of peribiliary enhancement at 2 and 3 min after gadolinium administration was assessed. Peribiliary hyperenhancement was defined as linear hyperenhancement within the hepatic parenchyma adjacent to the bile ducts including the bile duct wall. Its degree was determined

based on the portion of the liver parenchyma displaying the greatest degree of peribiliary enhancement and it was scored as described in the table 1.

Table 1. Classification of degree of peribiliary enhancement after gadolinium administration used by Petrovic *et al.*[131]

Classification of peribiliary enhancement	Features
None	No peribiliary enhancement obserbved
Minimal	< 2 mm margin of enhancement surrounding the bile ducts
Moderate	2-6 mm margin of enhancement surrounding the bile ducts
Marked	> 6 mm margin of peribiliary enhancement

Their data showed the absence of a strong linear relationship between the revised Mayo Risk Score and EHBD, IHBD findings and degree of peribiliary enhancement but the existence of a weak correlation between delayed (3 min after gadolinium administration) peribiliary enhancement with the revised Mayo risk score [131]. Subsequently, Ni Mhuircheartaigh *et al.* reported in 62 patients with PSC, the existence of a correlation between the arterial peribiliary enhancement and the revised Mayo risk score. The degree of involvement of peribiliary hyperenhancement was classified according to the criteria included in table 2.

Table 2. Classification of degree of involvement of peribiliary hyperenhancement after gadolinium administration used by Ni Mhuircheartaigh *et al.*

Degree of involvement of peribiliary hyperenhancement	
Localized	Less than 50% of a segment
Segmental	At least 50% of a segment but still confined to a single segment
Diffuse	Multiple segments

The interobserver agreement was very good for the presence of arterial peribiliary hyperenhancement, but fair for the extent of peribiliary hyperenhancement. An overall difference of arterial hyperenhancement among the three different Mayo risk score subgroups was reported but no differences were observed between patients in high and intermediate risk group. Moreover, they showed a significant difference in mean transplant-free survival according to the presence of arterial peribiliary hyperenhancement. A Cox

regression analysis to confirm the prognostic value of arterial peribiliary enhancement was not performed [132].

Spleen size

The baseline measurement of the maximal diameter of the spleen by means of cross-sectional imaging, ultrasound and magnetic resonance imaging, was found to be useful for diagnosis cirrhosis and to stratify PSC patients according their risk for developing clinical outcomes (cirrhosis decompensation, liver transplant and death) [133]. Moreover, spleen length measurement had a similar performance to transient elastography for the prediction of clinical outcomes [134].

Histological features

Small duct PSC

Patients with small duct PSC, as previously described, have a significantly longer transplant-free survival compared with patients with large ducts PSC [11,14,47–51] and the subtype of PSC (small duct *vs.* large duct) has been incorporate in the recently published Amsterdam-Oxford prognostic risk score [108].

Histological stage

The first study that reported on the prognostic role of histological stage in PSC was published in 1989. In this study, histological stage evaluated according Ludwig criteria was independently associated with survival [118].

More than 25 years after, a study including 64 Dutch patients from different centers assessed and compared the prognostic value of three histological scoring systems, namely Ishak, Nakanuma and Ludwig staging systems. The three staging systems were strongly associated to transplant-free survival and to the time to liver transplant, but they were not associated with cirrhosis decompensation. Nakanuma staging system had the highest hazard ratios associated to the first two endpoints. Moreover, Ishak and Nakanuma grading systems were not associated to any of the defined endpoints. Third, in Nakanuma staging system, the degree of fibrosis and the deposition of orcein granules, but not bile duct loss, were independently associated to transplant-free survival and time to liver transplant. The fourth relevant observation is that the three histologic staging system demonstrated only a weak correlation with biochemistry [135]. These data were subsequently validated in an International multicentric cohort composed by 119 PSC patients from seven European centres. Six independent pathologists examined all liver biopsies by evaluating the three histological scoring systems cited above. The results showed that the three staging system were independent predictors of transplant-free survival and liver-related events. Moreover, Nakanuma staging system was also independently associated to the composite endpoint that combine liver transplant and PSC-related death. Deposition of orcein granules has the highest hazard ratio compared to the other component of Nakanuma staging system. The interobserver agreement was substantial for Ludwig stage and Ishak stage and moderate for Nakanuma staging system. This was mainly due to the moderate agreement in the evaluation of the orcein deposition despite a substantial agreement for Nakanuma component fibrosis. The absence of a strong correlation between histological stage and biochemistry was also confirmed. Finally, Nakanuma grading system was negatively associated with transplant-free survival and the cholangitis activity grade had the highest protective association. The interobserver variability for Nakanuma

grade was moderate and this was mainly due to a slight interobserver variability of cholangitis activity evaluation [136].

Elastography

Liver stiffness by transient elastography

Liver stiffness (LS) measurement based on vibration controlled transient elastography (TE) is a powerful marker of chronic liver disease assessment and it has been shown to correlate with histological fibrosis stage and severity in various chronic liver disease. In two cohorts, including 28 and 73 French patients, LS was found to be independently associated to the stage of fibrosis documented by liver biopsy using METAVIR-derived scoring system [137,138] and TE had a high diagnostic accuracy for identifying severe fibrosis and cirrhosis [138]. Moreover, baseline LS and the progression rate of LS used as continuous markers of the liver state were correlated with long-term clinical outcomes in a cohort of 141 large duct PSC patients. Indeed, using an optimal cut off of 11.1 kPa, TE, was able to distinguish patients with different risk to develop the composite endpoint (LT, liver related death and cirrhosis complications), with an associated hazard ratio of 7.3 (95% CI, 2.9-18.1, $p < 0.001$). The change in LS was also independently associated to the composite endpoint with an associated hazard ratio of 11.8 (95% CI 2.7-52.2, $p= 0.001$) for the optimal cut off value of 1.5 kPa/year. Finally, LS was compared to other biochemical variables (bilirubin, ALP, AST..). Bilirubin together with LS were the two variables independently associated to endpoint-free survival as well as changes in LS[138]. The performance of TE measurement for the diagnosis and exclusion of higher fibrosis stages and cirrhosis was also confirmed in a cohort of 62 German patients and its prognostic value was confirmed in a combined collaborative cohort of 130 German and French patients

and resulted comparable to that of spleen length measurement. In this study, the optimal cut off of LS for the prediction of clinical events (cirrhosis decompensation, liver-related death or LT) was 12.4 KPa [134]. Overall, these results confirmed the prognostic value of LS in PSC but a number of factors need to be taken into account while interpreting the results of TE. Indeed, in PSC patients the presence of severe extrahepatic strictures, an elevated total bilirubin and/or transaminases serum level, a recent food intake or the presence of acute bacterial cholangitis could overestimate the LS value [139].

Liver elasticity by magnetic resonance elastography

Liver stiffness could be also assessed using magnetic resonance elastography (MRE) which offers a number of advantages compared to the transient elastography including the evaluation of a larger volume of the liver, the simultaneous evaluation of cholangiographic and parenchymal features of the disease in the same examination, a lower failure rate compared to TE and lack of influence of obesity [140]. A study including 266 patients documented that LS by MRE was significantly associated with the endpoint represented by hepatic decompensation (hazard ratio 1.55; 95% CI, 1.41-1.70) and both LS and Mayo risk score were independently associated to the endpoint by adjusted multivariate analysis. The cumulative incidence of hepatic decompensation was significantly different between the three subgroups of risk of patients identified by LS values (< 4.5 kPa, 4.5-6.0 kPa, > 6.0 kPa) [140]. Analysing 20, among 266, PSC patients with available liver biopsy, authors reported that liver stiffness by MRE has a good diagnostic performance compared to liver biopsy to identify severe fibrosis or cirrhosis.

Composite scores

Eleven composite prognostic score have been evaluated in patients with PSC, of them nine are PSC-specific [13,108,113–118,141] and the other two, Child-Pugh and MELD, are used to predict prognosis in cirrhosis of various aetiology and their use is limited to late stage disease [120,119].

Mayo risk score

The original Mayo risk score was the first proposed composite score in PSC, created to evaluate the risk of death for any cause. This score was built on a large cohort of 174 patients with a long-term follow-up (mean 6 years, range 2.7 - 15.5) and histological staging available at inclusion, scored according to the Ludwig criteria. The score was composed by the following 5 variables, independently associated to survival by multivariate analysis: age, serum bilirubin concentration, blood haemoglobin concentration, presence of absence of IBD and histological stage.

The risk score was computed according to the formula:

$R = 0.06 \times age(years) + 0.85 \times \log_e [minimun\ (bilirubin\ mg/dl\ or\ 10)] - 4.39 \times \log_e [minimum\ (haemoglobin\ mg/dl\ or\ 12)] + 0.51 \times biopsy\ stage + .\ 1.59 \times indicator\ for\ IBD$

Three risk groups with different observed survival were identified[118].

The main limits of this score, besides the invasive nature of the liver biopsy, were the exclusion of liver transplant from the endpoint, since it represents a major clinical event in the natural history of these patients, and the inclusion of deaths for all-causes.

King's college score

In 1991 Farrant *et al.* described the natural history of 126 PSC patients with a median follow-up time from diagnosis of 3 years (0.16-12.5 years) and they derived a prognostic score based

on variables independently associated to transplant-free survival. Only liver-related deaths were included in the endpoints. Features independently associated with survival were: hepatomegaly (H), splenomegaly (SP), serum ALP (A), histological stage (ST) and age. These features were combined in a prognostic index based on the following formula:

Prognostic index = 1.81 x H + 0.88 x SP + 2.66 x log (A) + 0.58 x ST + 0.04 x age

Besides the invasive nature of histological stage, another limit of this score is the presence of two variables, hepatomegaly and splenomegaly, with subjective criteria of evaluation [113].

Multicenter Model

The multicenter model was built using data of 426 PSC patients from 5 medical centers with a median follow-up time of 3.0 years (range 0.1-16.6 years) and the endpoint was liver transplant or death for any cause. Four variables were independently associated with transplant-free survival (bilirubin, stage, age, splenomegaly) and were combined in the formula:

*R=0.535 *log_e bilirubin +. 0.486*histological stage + 0.041* age+0.705*splenomegaly.*

This score was able to distinguish between three risk groups of patients with different survival and confidence intervals for predicting patient-specific survival probabilities were also reported [117]. The limit, as for the previous models, was the inclusion in the score of histological and subjective variables.

Scandinavian Model

Broomé *et al.* in 1996 reported on natural history of 305 Swedish patient followed-up for a median time of 63 months (range 1-194 months) and built a prognostic score able to predict

the endpoint (death for liver cause or liver transplant). The score was based on histological stage, age and bilirubin and it was calculated according the following formula:

PI= 0.24 x histology stage + 0.03 x age + 0.49 x log_2 bilirubin

They plotted the estimated survival against this prognostic index and they suggested its usefulness for the timing of transplantation and for patient counselling [141] .

Revised Mayo risk score

The Revised Mayo risk score was calculated in order to create a natural history model for the disease based on routine clinical findings without the need for liver biopsy. This score was built based on the multicentric cohort used to derive the Multicenter model [117] and the endpoint here was death from any cause and a complex adaptation of median survival for transplanted patients was carried out. The final model was composed by 5 variables (age, total bilirubin, albumin, AST and previous variceal bleeding) and was calculated by the following formula:

*R = 0.03*age + 0.54*log(bilirubin[mg/dL]) +0.54*log(AST[U/L]) + 1.24*(variceal bleeding[0/1]) -0.84(albumin[g/dL]).*

In the same study authors used the risk score to obtain survival estimates up to 4 years of follow-up and they validated the model in an independent group of 124 patients [116]. These, together with non-invasive determination of the variables included in the model, represented the strengthens of this score and the reasons for its diffuse use worldwide.

Time-dependent score

Taking into account the variability of the disease course, a multicentric group built a prognostic model that combined time-fixed and time-dependent Cox regression analysis using

consecutive clinical and laboratory follow-up data from the diagnosis of 330 PSC patients from 5 European centers followed-up for a median of 8.4 years. They derived a time-dependent prognostic model combining bilirubin (on a logarithmic scale), albumin and age at diagnosis of PSC that appeared to be more precise in estimating short-term survival than time-fixed model [115]. A strength of this study is that it included an internal cross-validation.

PSC score

A cohort of 273 German PSC patients followed up for a median time of 76 months (range 1-280 months) was used by Tischendorf *et al.* to derive a prognostic model to predict LT- free survival. The final model, based on the results of multivariate analysis, was composed by age, albumin, the persistent bilirubin alteration for > 3 months, the presence of hepatomegaly, splenomegaly, dominant bile duct stenosis and the presence of intrahepatic and extrahepatic ductal changes at ERCP [13]. This model was able to distinguish five risk classes of patients with different survival but its use in clinical practice was limited by the presence of subjective variables and the invasive assessment of cholangiographic findings.

Amsterdam-Oxford risk score

The Amsterdam-Oxford risk score is a novel prognostic score associated to transplant-free survival derived in a cohort of 692 PSC patients from Netherland and validated in an external cohort of 264 PSC patients from Oxford, UK, with a comparable median follow-up of 110 months (interquartile range 69-184) and 103 months (interquartile range 53-153), respectively. The end-point in this study was time to death for liver-related causes or liver transplant. The model combines simple clinical and biochemical variables: PSC subtype (large duct *vs.* small duct), AST, ALP, total bilirubin (expressed in x ULN and transformed to [10-log]),

albumin (expressed in x LLN and transformed to [10-log]) and platelets (expressed in x LLN and transformed to abs[10-log-0.5]). As output, the model provides an absolute value and the 5-year, 10-year and 15-year survival probabilities. The performance of the model was tested by using data at 1, 2 and 3 years of follow-up from diagnosis. The C-statistics of the model is moderate, 0.69 (95% CI 0.51 to 0.85), and it similar when using data collected during the first 3 years from diagnosis. Four risk categories based of optimal threshold with different survival were identified in the derivation cohort and then their discriminating value was confirmed in the validation cohort. No data regarding the negative and positive predictive factors of the different risk categories was provided. The evaluation of the prognostic value of the Amsterdam-Oxford risk score in an external cohort composed by patients followed up in different IPSCSG centers using data after the first 3 years of follow-up is now ongoing with the contribution of the author of this thesis and preliminary results will be communicated to the Liver Meeting® by AASLD in November 2018.

PREsTO

The Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTO) is the last published prognostic model. This is the first model built based on machine-based learning technique. The model was derived using data from 509 PSC patients from North America and then validated in an International multicentric cohort of 278 PSC patients. The endpoint of this study was cirrhosis decompensation. The variables identified, by gradient boosting, to be associated to the endpoints were serum bilirubin, albumin, ALP (x ULN), platelets, AST, haemoglobin, sodium, patient age and the number of years since the diagnosis of PSC. Up to know, the formula for the calculation of this score has not yet been published. The C-statistic of PREsTO in the validation cohort for prediction of hepatic decompensation was 0.90 (95%CI 0.85-0.59). The

tool performed well when compared to MELD score and Mayo risk score, both in patients without advanced disease and in the same patients, later in disease course [114]. Thus, this score offers a number of advantage that may overcome the limits reported for the previously published scores.

CHAPTER 4

The role of magnetic resonance imaging in primary sclerosing cholangitis

Nora Cazzagon

THE ROLE OF MAGNETIC RESONANCE IMAGING IN PRIMARY SCLEROSING CHOLANGITIS

MRI was introduced in the '90 in the diagnostic process of patients with PSC, because it allows a good visualization of biliary tree without the need of invasive catheterization. Indeed, by using heavily T2-weighted (T2w) sequences, the signal of static or slow-moving fluid-filled structures, such as the bile and pancreatic ducts is greatly increased, resulting in increased contrast compared with the background and thus allowing a clear depiction of the bile ducts. Moreover, when combined with conventional T1- and T2w sequences, MRI allows anatomic imaging of extraductal disease.

MRI offers a number of advantages over ERCP in biliary tree examination and this determined a large utilization of this technique in the last 20 years in patients with suspected bile ducts disease or in the follow-up of these patients.

The main advantages of MRI over ERCP are the following: (**1**) MRI is a non-invasive technique; (**2**) is more cost-effective; (**3**) uses no ionizing radiation; (**4**) requires no anaesthesia; (**5**) is less operator dependent; (**6**) better visualizes ducts proximal to an obstruction or tight stenosis; (**7**) allows anatomic imaging of extra ductal disease.

On the other hand, MRC has less spatial resolution than ERCP, thus decreasing the sensitivity to peripheral ductal abnormalities which may be not visualized due their physiologic, non-distended state. A meta-analysis comparing 6 prospective study that evaluated the diagnostic performance of MRC in PSC showed that this technique has a high sensitivity and specificity for the diagnosis of PSC, 86% and 94% respectively, without the risk of ERCP. Moreover, MRC as initial test strategy for diagnosis PSC is cost-saving compared to ERCP [36].

European guidelines [38] recommended MRI/MRCP:

1. As the primary diagnostic modality in case of suspicion of PSC;
2. Before therapeutic ERCP in patients with established PSC.

Moreover, the International PSC study group, in a position statement, suggested [68]:

3. To perform an MRI/MRCP if a concern of CCA develops, before invasive procedure (ERCP or percutaneous cholangiogram);
4. To perform an MRI/MRCP including contrast media within 6 months from the diagnosis, if the initial MRI/MRCP at the time of establishing a PSC diagnosis has been performed without contrast because of the higher risk of prevalent CCA when PSC is detected;
5. Many experts, despite the absence of evidence supporting or refuting CCA screening, recommend regular CCA screening with MRI/MRCP in PSC patients.

Technical aspects of MRI in PSC

MRCP uses high-strength magnets (1.5-3 T) and, due to the high T2W signal intensity of bile compared to surrounding strictures, provides a detailed visualization of the biliary tree and the pancreatic duct without the need of contrast agents to obtain a cholangiogram. Fasting is a requisite to perform MRCP and oral administration of pineapple juice or diluted gadolinium contrast (1ml in 200 mL of water) is recommended in order to suppress the signal of stomach and duodenal content [68]. Three-dimensional (3D) MRCP using 1-mm thickness slices provides a higher spatial resolution and an excellent signal/noise ratio compared with two-dimensional (2D) MRCP and it is now preferred compared with 2D-MRCP for the diagnosis of PSC. Indeed, the reduction of the thickness of slices and the suppression of noise allows a relevant post-processing of images to obtain maximum intensity projection images (MIP) and multiplanar

reformatted images (MRP). These two types of images enable both the spatial visualization of the biliary tree and the evaluation of small abnormalities of the biliary tree [142]. On the other hand, 2D-sequences have shorter acquisition than 3D-sequences, this limits the occurrence of motion artefacts and it enable its use in patients with low compliance for breath hold. Moreover, 2D-MRCP could be interpreted immediately without post-processing [142].

Other complementary sequences are used to complete the MRI of the biliary tree. T1 weighted (T1w) fat suppressed sequences are used to assess the presence of intrahepatic calculi (in the majority of cases hyperintense due to the presence of haemoglobin degradation products) and to evaluate liver parenchymal dysmorphy, splenomegaly and signs of portal hypertension.

Moreover, the use of gadolinium-based contrast agent (GBCA) during MRI could add information regarding biliary wall and liver parenchyma. Based on the type of biodistribution, GBCA used in MRI for the assessment of biliary diseases, are distinct in extracellular agents (e.g. Gadopentetate Dimeglumine, Magnevist®, Bayer Schering Pharma, Gadoterate meglumine, Dotarem®, Guerbet) and hepatospecific agents (e.g. Gadoxetate disodium, Primovist®or Eovist®, Bayer Schering Pharma, Gadobenate dimeglumine, MultiHance®, Bracco). While extracellular GBCA are cleared primarily by renal filtration, 50% of the hepatospecific GBCA are rapidly taken up by the hepatocytes and excreted into the bile with a peak of biliary enhancement approximately 20 minutes after the injection. At this time T1w-MRCP are performed. Despite T2w-MRCP has a higher spatial resolution in peripheral ducts compared with both T1w-MRCP [143,144] and ERCP [145], T1w-MRCP provides a more accurate visualization of central stricture compared to T2w-MRCP [144] and could add diagnostic information regarding parenchymal function. Indeed, by using hepatospecific GBCA and dynamic T1w sequences including the hepatospecific phase, a local or diffuse impairment of

liver parenchyma and alterations of the excretion of the contrast in the common bile duct could be visualized [144]. In patients with PSC the excretion of the hepatospecific GBCA is delayed compared with healthy controls and the excretion of the contrast correlates with the degree of hepatic function evaluated by bilirubin level [146].

Moreover, T1w fat suppressed sequences before and after GBCA injection may demonstrate the presence of biliary wall thickening and mural enhancement of the biliary ducts after injection and the presence of wedge-shaped alteration of the liver parenchyma. These last are due to the presence of confluent fibrosis and they appear typically hypointense in T1w sequences in the pre-contrast phase compared with the surrounding parenchyma and they increase signal during arterial and portal phase. In the delayed phase their signal intensity continues to increase when extracellular agents are used, differently, they become hypointense compared with surrounding parenchyma when hepatospecific agents are used and they further decrease intensity in the hepatospecific phase. This pattern is caused by the lower presence of hepatocytes within the confluent area of fibrosis compared with the surrounding parenchyma, which thus accumulates in the hepatospecific phase, a higher quantity of contrast compared with the focal area of fibrosis [147]. These wedge-shaped area have been also visualized, by using T2w sequences before and after GBCA injection with quantification of the relative liver enhancement [148]. Other studies aimed to determine whether a dynamic MRI with hepatospecific GBCA was able to discriminate between different stage of fibrosis but no definitive results were provided [149,150].

The use of contrast agents is not mandatory for the diagnosis of PSC but, as reported above, it is recommended in case of suspicion of CCA and over the first 6 months from PSC diagnosis in order to improve the diagnostic performance of prevalent cases of CCA. The position statement by the International PSC Study Group identified a minimum and a complete

standard protocol for the diagnostic workup of patients with suspected PSC. The minimum standard protocol includes: T2-weighted MRCP (better 3D- over 2D-MRCP), T1- and T2-weighted axial sequences for the visualization of liver parenchyma. The complete protocol, by adding sequences after GBCA injection, includes: T1 contrast dynamic sequences with arterial, portal venous and parenchymal phase, T1 weighted MRCP and T1 weighted hepatobiliary phases, these last two when hepatospecific contrast agents are used [68]. At the moment there are no evidences to prefer the use of extracellular or hepatospecific GBCA.

Other MR techniques could add information to classic MRI sequences and for these reasons they could be included to the MRI protocol.

Magnetic resonance elastography, as previously reported, enables the assessment of liver fibrosis of the whole parenchyma[68,140]. Moreover, diffusion-weighted imaging (DWI), could also be included in the complete protocol of MRI in patients with PSC[68] since a recent study suggested that DWI correlates with fibrosis assessed by transient elastography, but it seems unable to distinguish moderate/severe fibrosis (F2-F3) from cirrhosis (F4)[149].

Cholangiographic and liver parenchymal changes in PSC

The first description of cholangiographic findings in PSC obtained during ERCP was published in 1983 and included 86 PSC patients, 16 patients with PBC and 82 patients with primary bile duct carcinoma. The presence of multifocal strictures involving both intra- and extrahepatic bile duct was found to be most common in PSC than in other groups and the typical “beaded” appearance of bile ducts characterized by diffusely distributed, short and annular strictures alternated with normal or slightly dilated segments was described. Moreover, the presence of band-like strictures, diverticulum-like out-pouching, diverticula without band strictures in 20%, 10% and 16% of PSC patients respectively, were also reported. Pancreatic duct

abnormalities were also documented in 3/40 patients [128]. Subsequent studies have combined these cholangiographic findings in order to classify different radiological subtypes of the disease [129,151]. One of the first proposed classification was that from Majoie *et al.* This was a descriptive, rather than quantitative, classification of bile duct anomalies [129]. This classification was subsequently adapted by Ponsioen *et al.* by adding the category 0 to distinguish intra- and extrahepatic disease and it was used to build the Amsterdam cholangiographic score (Table 3)[106].

Table 3. Classification of cholangiographic findings in PSC according Majoie and modified by Ponsioen *et al.*[106]

Type of duct involvement/classification	**Cholangiographic abnormalities**
Intrahepatic	
0	No visible abnormalities
I	Multiple calibre changes; minimal dilatation
II	Multiple strictures, saccular dilatation, decreased arborisation
III	Only central branches filled despite adequate filling pressure; severe pruning
Extrahepatic	
0	No visible abnormalities
I	Slight irregularities of duct contour; no stricture
II	Segmental stricture
III	Stricture of almost entire length of duct
IV	Extremely irregular margin; diverticulum-like outpouchings

In the same year of Majoie classification, a quantitative classification of bile duct anomalies was proposed (Table 4). The advantage of this classification was the presence of objective criteria to defined different cholangiographic findings and the clear localization of the lesions.

Table 4. Classification of cholangiographic findings in PSC used by Craig *et al.*[126]

Characteristic	Classification
Bile duct strictures	
Grade	1: 0-25% narrowing of duct 2: > 25-50% narrowing of duct 3: > 50-75% narrowing of duct 4: > 75-100% narrowing of duct
Length	Band: 1-2 mm of involvement Segmental: 3-10 mm of involvement Confluent: > 10 mm of involvement
Extent	Localized: ≤ 25% of ducts involvement Diffuse: > 25% of ducts involvement
Bile duct dilatation	
Common bile duct	None: < 15 mm Mild: 15-19 mm Marked: ≥ 20 mm
Left Main Hepatic Duct	None: < 7 mm Mild: 7-9 mm Marked: ≥ 10 mm
Right Main Hepatic Duct	None: < 6 mm Mild: 6-7 mm Marked: ≥ 8 mm
Secondary intrahepatic ducts	None: < 4 mm Mild: 4 mm Marked: ≥ 5 mm

Other cholangiographic findings in PSC are the presence of primary pigmented intraductal stones in up to 30% of PSC patients [152], moreover, some authors suggested that a retracted papilla, visualized at ERCP or MRCP, is a specific sign of PSC but these data have not yet been confirmed in external cohorts [153,154]. Finally, the presence of biliary cystic dilatation in the intrahepatic bile ducts was also documented in 6 patients with PSC [155–160] and in 5 explanted liver [161].

The first description of magnetic resonance findings in a small cohort of PSC patients was reported in the late nineties and it showed an adequate diagnostic performance of this technique compared with ERCP. By applying the Majoie classification of bile duct anomalies to MRI, the authors reported an overestimation of intrahepatic disease in 5% of patients and both an over- and underestimation of extrahepatic disease in 10% of patients compared with

ERCP [162]. Subsequently, a number of studies reported on the use of MRCP in PSC confirmed the high diagnostic accuracy of this technique[89,143,145,163,164].

As previously cited the advantage of MRI over ERCP consists in the possibility to describe the morphological alterations of liver parenchyma. The presence of peripheral wedge-shaped areas of parenchymal atrophy (also called confluent focal fibrosis, focal atrophy) have been largely reported and these area are not invariably associated to the cirrhotic stage [165]. Actually, focal atrophy likely represents a consequence of the progression of focal fibrosis surrounding bile duct up to the obliteration of the duct and subsequent impairment of cholestasis, inflammation and thus the development of focal fibrosis of the liver parenchyma [142].

The presence of biliary wall thickening and mural contrast enhancement of the biliary ducts have been also reported and they could be possibly related to inflammatory processes [142].

CCA is an unpredictable complication of PSC, since is not correlated with an advanced disease. No cholangiographic features are pathognomonic of CCA, and despite the majority of CCA occurred in common hepatic duct or at the bifurcation representing Klatksin's tumour, a number of CCA arise in the intrahepatic bile ducts, but no precise information regarding the CCA localization in PSC patients are available. As reported by MacCarty *et al.,* cholangiographic features suggesting CCA are the presence of irregular high grade ductal narrowing with irregular edges, the rapid progression of strictures, the presence of marked ductal dilatation proximal to the strictures, and the presence of polypoid lesions, especially those larger than 1 cm in diameter [166]. Compared to ERCP, MRI and computed tomography offers the advantage to allow the evaluation of the extra ductal extent and thus a better staging of the tumour [152]. Moreover, since most of CCA has a fibrous core, a delayed enhancement and washout after GBCA injection could be observed and this finding is nearly 100% specific for CCA [68]. Cross-sectional imaging is fundamental for tumour staging, to assess its resectability and MRI

appeared to be superior to CT for the detection of cholangiocarcinoma [167]. Moreover, by adding GBCA injection during MRI the sensitivity of the technique for CCA detection is increased [95].

Magnetic resonance imaging for evaluation of disease evolution and prognosis

As summarized above, MRI and associated techniques, might offer a number of possible applications in PSC other than the diagnosis, such as the staging of the disease and the evaluation of liver function. Moreover, a follow-up with MRI could hypothetically be useful not only for the surveillance of hepatobiliary malignancies but also to assess, as reported for ERCP, the dynamic changes of the disease over time and their eventual correlation with clinical outcomes.

For these reasons in the last few years, a great interest regarding the prognostic role of MRI, has been developed and it represents an open issue of this disease [68].

In the clinical practice, we commonly observe that a number of patients shows a clinical and biochemical stability over time for many years. Moreover, since the early '90 is known that a percentage of PSC patients without malignant complications have stable cholangiographic findings during follow-up [129].

The radiological stability in a percentage of PSC patients was recently reported by Ruiz *et al.* that analysed subsequent annual 3D-MRCP and liver MRI of 64 PSC patients [90]. They observed that the progression of radiological features was present in 58% of patients and in the remaining patients the morphology was stable over time. Their aim was to assess whether any of the radiological features were independently associated to radiological progression.

The major strength of this study is that it proposed and it applied a standard model of interpretation of cholangiographic and parenchymal changes of PSC by using an adaptation of

the Craig's quantitative classification of cholangiographic findings [126] and the Petrovic's quantitative classification of biliary wall enhancement after GBCA injection [131]. This is the first model proposed to describe MRI features in PSC and it has the relevant advantage to offer a quantitative assessment of the lesions (Table 5), thus this model could ameliorate interobserver variability and improve the diagnostic performance of MRI in PSC. By multivariate analysis and using sequences after GBCA injection, they reported that intrahepatic bile duct dilatations, dysmorphy, portal hypertension and a heterogeneous parenchymal enhancement were independently associated to radiological progression. Moreover, two MRI risk scores, called "Anali score", were built according the following formula:

Anali score without gadolinium = (1 x portal hypertension) + (2 x dysmorphy) + (1 x IHBD dilatation)

The range of possible score of Anali score without gadolinium was 0 to 5 and 3 was the optimal cutoff in this population associated with the highest risk of radiological progression.

Anali score with gadolinium = (1 x dysmorphy) + (1 x parenchymal enhancement heterogeneity)

The range of possible score of Anali with gadolinium was 0 to 2 and 1 was the optimal cutoff in this population associated with the highest risk of radiological progression[90].

The authors did not provide information regarding the prognostic value of radiological progression and the prognostic value of these two scores.

Table 5. Standard model of interpretation by Ruiz *et al.*[90]

Feature	Points
CBD stricture	0= no stricture; 1= stricture ≤ 75% ; 2= stricture >75%
CBD stricture length	0= absent; 1=band (stricture <2mm); 2= segmental (stricture 2-10mm) ; 3= confluent (stricture >10mm)
CBD dilatation	0= none (≤10mm); 1=mild (11-14mm); 2= marked (≥15mm)
CBD enhancement	0=absent; 1= thickness<2mm ; 2= thickness 2-6mm ; 3= thickness>6mm
RHD stricture	0= no stricture; 1= stricture ≤ 75% ; 2= stricture >75%
RHD stricture length	0= absent; 1=band (stricture <2mm); 2= segmental (stricture 2-10mm); 3= confluent (stricture >10mm)
RHD dilatation	0= none (≤6mm); 1=mild (7-8mm) ; 2= marked (≥9mm)
RHD enhancement	0=absent; 1= thickness<2mm ; 2= thickness 2-6mm ; 3= thickness>6mm
LHD stricture	0= no stricture; 1= stricture ≤ 75% ; 2= stricture >75%
LHD stricture length	0= absent; 1=band (stricture <2mm); 2= segmental (stricture 2-10mm) ; 3= confluent (stricture >10mm)
LHD dilatation	0= none (≤6mm); 1=mild (7-8mm) ; 2= marked (≥9mm)
LHD enhancement	0=absent; 1= thickness<2mm ; 2= thickness 2-6mm ; 3= thickness>6mm
IHBD stricture	0= no stricture; 1= stricture ≤ 75% ; 2= stricture >75%
IHBD liver involvement	0= absent; 1= localized (≤25% IHBD involved); 2= diffuse (>25% IHBD involved)
IHBD dilatation	0= none (≤3mm); 1=mild (4mm) ; 2= marked (≥5mm)
IHBD enhancement	0=absent; 1= thickness<2mm ; 2= thickness 2-6mm ; 3= thickness>6mm
Parenchymal enhancement heterogeneity	0= absent ; 1=present
Intraductal stones	0= absent ; 1= present
Dysmorphy	0= absent ; 1= present
Portal hypertension	0= absent ; 1= present
Gallbladder size	0= absent ; 1= normal ; 2= dilated
Lymph nodes	0= absent ; 1= present

Abbreviations: CBD, Common bile duct; RHD, right hepatic duct; LHD, left hepatic duct; IHBD, intrahepatic bile ducts. Definitions: Portal hypertension was defined by the presence of portosystemic shunts with or without splenomegaly. Gallbladder size: normal size is defined by ratio length/width ≥ 2, dilated is defined by presence of biconvex contours or ratio length/width < 2. Lymph nodes: present if supracentimetric size or enlarged number.

Two studies published in 2018 reported on the possible prognostic role of MRI findings in PSC. Tenca *et al.* by evaluating simultaneous MRI and ERCP of 48 PSC patients evaluated the association between bile duct changes and markers of PSC disease activity and severity and the association between peribiliary enhancement and markers of disease activity. They reviewed all MRI and ERCP and scored the findings using the modified Amsterdam score, and

compared biliary findings found with both ERCP and MRCP. A high overall agreement between ERCP and MRCP in detecting any PSC changes was reported both for IHBD and EHBD. But a moderate agreement was reported when the Amsterdam score was applied, due to a significant difference between ERCP and MRCP in the evaluation of EHBD. Intrahepatic score evaluated by ERCP correlated with CA19-9, but none further correlation between ERCP score and any other markers of disease severity was documented. When applying MRCP score, correlations between IHBD score and ALP and CA19-9, and between extrahepatic score and CA19-9 were reported. Only MRCP score for EHBD weakly correlated with clinical outcomes (death, liver transplant). Finally, peribiliary enhancement weakly correlated with cytologic classification but not with any other markers of disease activity [97]. The moderate agreement between ERCP and MRCP in the evaluation of disease severity by using Amsterdam score, was due to an overestimation of severity of the EHBD changes by MRCP. We might suggest that the overestimation of EHBD strictures by MRCP compared to ERCP is probably caused by the physiologic state of bile ducts during MRCP compared with the distended state subsequent to contrast agent injection during ERCP. These evidences suggest that the modified Amsterdam score is not a good candidate for estimating disease severity and eventually prognosis by MRCP in PSC.

Schulze *et al.* recently reported on 111 PSC patients the correlation between the relative enhancement of liver parenchyma (RLE) after hepatospecific contrast agent (Primovist®), liver function tests and outcome. Relative enhancement in the hepatospecific phase negatively correlated with ALP and bilirubin and positively correlated with INR [168]. Moreover, a negative correlation between RLE and the biochemical prognostic risk scores (i.e. Amsterdam-Oxford model score, MELD score and the Mayo risk score) was documented. Finally, RLE correlated with all clinical endpoints (development of CCA, LT and death for liver-related cause) and with

survival [168]. No information regarding the independent value of RLE in predicting clinical outcome was provided.

Pooling together these three studies, the results suggest that MRCP with MRI is a promising tool to assess disease severity, progression and probably prognosis in PSC patients and the research in this field is justified.

Open points on the use of magnetic resonance imaging in PSC

There are a number of open questions regarding the use of MRI in PSC patients. The first, is the lack of agreement also among experts regarding the model of interpretation of cholangiographic changes of the disease and their clinical relevance. As recently point out by Zenouzi *et al.* there is a wide variability in the MRCP interpretation among different experts (radiologists, gastroenterologist, hepatologist) regarding the severity of bile ducts changes and the indication to perform an ERCP with therapeutic purposes [169]. The use of the standard model of interpretation by Ruiz *et al.* could represent a relevant tool to standardize the description of PSC lesion and could be used to assess clinical and prognostic correlation.

Secondly, differentiating benign and malign strictures in PSC represents a relevant issue, and the evaluation of the prospective utility of MRI/MRCP in this field is warranted.

As a third point, biliary wall enhancement after GBCA injection has demonstrated a weak correlation with prognosis, but the correlation between biliary wall enhancement and histology has not been reported so far. Indeed, it could be useful to determine whether the presence and the pattern of biliary wall enhancement are correlated to a more inflammatory or fibrotic content and thus identifying targets for new therapies and for monitoring therapeutic response.

Another relevant open issue regards the use of GBCA during subsequent MRI since in the last years several studies demonstrated the accumulation of GBCA in the brain, attested by the presence of high-T1 signal intensity at the level of nucleus dentatus and globus pallidus. The accumulation appeared directly correlated to the number of administrations of GBCA [170] and in the majority of cases this was correlated to the use of linear agents, even if the autoptic confirmation of GBCA deposition in the brain was also documented for macrocyclic agents [171]. Moreover, by increasing the number of GBCA administrations, its deposition was described also in other brain regions. The clinical implications of GBCA deposition in the brain have not yet been elucidated but at the moment no evidences that gadolinium deposition has caused any harm to patients exists. The European Medicine Agency on July 2017 completed the revision of information regarding GBCA and provided recommendations to restrict authorization of some GBCA (Gadopentetic acid, Magnevist® only for intra-articular use, Gadobenic acid, Multihance® only to liver scans) and to suspend the authorizations of others linear GBCA (Gadopentetic acid, Magnevist®, Gadodiamide Omniscan ®, Gadoversetamide, Optimark®) [172]. The Italian Medicine Agency (AIFA) on 28 February 2018 suspended the authorization of linear GBCA except for Gadoxetic acid and Gadobenic acid which remains available only for liver scan, and in general, recommended its use only in case of evident diagnostic needs and at the lowest possible dose [173]. Thus, it's clear that the benefit of linear GBCA injection in subsequent MRI in PSC patients will need to be weighed against the risk of its deposition in the brain.

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CHAPTER 5

Aims of the thesis

Nora Cazzagon

AIMS OF THE THESIS

The aims of this thesis were to investigate the prognostic role of MRI in patients with PSC.

The primary aim was to investigate the prognostic value of the two MRI risk scores in a derivation cohort and to validate the results in an external multicentric cohort.

The secondary aims were:

- To evaluate whether the use in combination of MRI risk score without GBCA injection and liver stiffness measurement by transient elastography may improve risk stratification in PSC patients.
- To evaluate the radiological and clinical course of PSC patients with intrahepatic bile ducts cystic dilatations and to evaluate the prognostic value of this MRI finding.
- To assess the existence of MRC, biochemical and clinical criteria of improvement after endoscopic treatment for dominant strictures in patients with PSC.

For each aim a correspondent project was designed and the results are here reported in the form of four original articles. Moreover, as introduction to the project regarding the predictive criteria of improvement after endoscopic treatment, a review summarizing previous studies on endoscopic treatment of dominant stenosis in PSC was included.

CHAPTER 6

Two simple magnetic resonance risk scores are able to predict prognosis in patients with primary sclerosing cholangitis

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ABSTRACT

Background and aims

PSC has a variable, often progressive course. MRC is the first-choice modality for diagnosis and two magnetic resonance (MR) risk scores, called Anali without and with gadolinium, are able to predict radiological progression. Our aim was to assess their prognostic value.

Patients and methods

We designed a retrospective multicentric international study comprising two cohorts of large-duct PSC patients: a derivation and a validation cohort. All the first available MR examinations were reviewed by two radiologists and the Anali scores were calculated: Anali without gadolinium = (1 x dilatation of intrahepatic bile ducts) + (2 x dysmorphy) + (1 x portal hypertension); Anali with gadolinium = (1 x dysmorphy) + (1 x parenchymal enhancement heterogeneity). The primary endpoint was survival without LT or cirrhosis decompensation. The prognostic value of Anali scores was assessed by Cox regression model.

Results

238 patients were included, in equal numbers (*i.e.* 119) in the two cohorts. During a median follow-up of 4.4 and 3.8 years, 8 and 5 patients died, 20 and 24 patients underwent LT and 18 and 24 patients developed cirrhosis decompensation, in the derivation and validation cohorts, respectively. In the univariate analysis, factors associated with survival without LT or cirrhosis decompensation in the derivation cohort were: bilirubin, AST, ALT, γGT, ALP, albumin and Anali scores. Predictive performances of Anali scores without and with gadolinium assessed by c-statistic were 0.89, $IC_{95\%}$[0.84-0.95] and 0.75, $IC_{95\%}$[0.64–0.87], respectively. Independent prognostic factors identified by multivariate analysis were Anali scores and increased bilirubin. The prognostic value of Anali scores was confirmed in the validation cohort.

Conclusion Anali scores can predict the clinical outcome in PSC patients.

INTRODUCTION

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 is often progressive, leading to biliary cirrhosis and its complications [1]. In addition, patients with PSC are exposed to an increased risk of CCA and other malignancies [2]. Overall, PSC is a severe disease and median transplant-free survival ranges from 13 years in patients seen at tertiary referral centres to 20 years in a population-based cohort [3,4]. 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. The clinical course of the disease is highly variable among patients. In the last 30 years many potential prognostic factors including clinical, biochemical, histological, elastographic and radiological features were examined [2]. Identification of prognostic factors is essential for tailoring the follow-up strategies and/or testing new therapeutic modalities in subgroups of PSC patients with poor prognosis. PSC specific clinical scores combining different single prognostic factors have been proposed and validated [2]. Nevertheless, clinical scores have several limitations, and none of them is recommended in the clinical practice for a single patient [5]. The recently proposed Amsterdam-Oxford prognostic model, combining seven objective and easily measurable variables, seems able to predict transplant-free survival [6]. Liver stiffness measurement appears to be a promising tool, since liver stiffness measured by vibration-controlled transient elastography at baseline, and the rate of liver stiffness progression, have been reported as strong predictors of prognosis in PSC [7]. As PSC is primarily a bile duct disease, the prognostic value of cholangiographic features has also been evaluated. The type and severity of cholangiographic changes assessed by ERCP have been correlated with prognosis in PSC [8], but the invasive nature of ERCP has limited its use to patients who need a therapeutic intervention. MRC,

combining high diagnostic performance and cost-effectiveness, together with non-invasiveness, is nowadays the modality of choice for diagnosis of PSC and it is recommended by international guidelines before ERCP [9]. A previous study, performed by our group in a cohort of 64 PSC patients, demonstrated that half of all patients displayed radiological progression during a mean follow-up of 4 years [10]. Radiological progression in these patients was independently predicted by the presence of severe intrahepatic bile ducts dilatation, dysmorphy, portal hypertension and parenchymal enhancement heterogeneity after gadolinium-based contrast agent (GBCA) injection. Using the combination of these radiological features, we built two MR risk scores (with and without GBCA administration), called Anali scores [10,11]. The aim of this study was to assess the clinical prognostic value of the two Anali scores in a derivation cohort of PSC patients and to validate these results in an external multicentric international cohort.

PATIENTS AND METHODS

We designed a longitudinal retrospective study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the protocol was approved by the ethic committee or institutional review board of all participating centres. Informed consent in writing was obtained from each patient according to the local ethical committee policy.

Inclusion criteria were the following: age at inclusion ≥ 18 years, diagnosis of large duct PSC, at least one liver MRI with MRC available for analysis, and at least one year of follow-up after the inclusion. The date of inclusion was defined as the date of the closest MR cholangiography to the diagnosis of the disease, available for analysis.

Exclusion criteria were the following: small duct PSC, autoimmune hepatitis/PSC overlap syndrome, previous LT, or significant hepatic comorbidities, such as associated hepatitis B or C infection, human immunodeficiency virus infection, or nonalcoholic steatohepatitis, secondary sclerosing cholangitis, cholangiocarcinoma, hepatocellular carcinoma and cirrhosis decompensation at the time of inclusion.

Study population

We used two different cohorts of PSC patients: a derivation cohort to assess the prognostic value of Anali scores and a validation cohort to confirm these results in an external population.

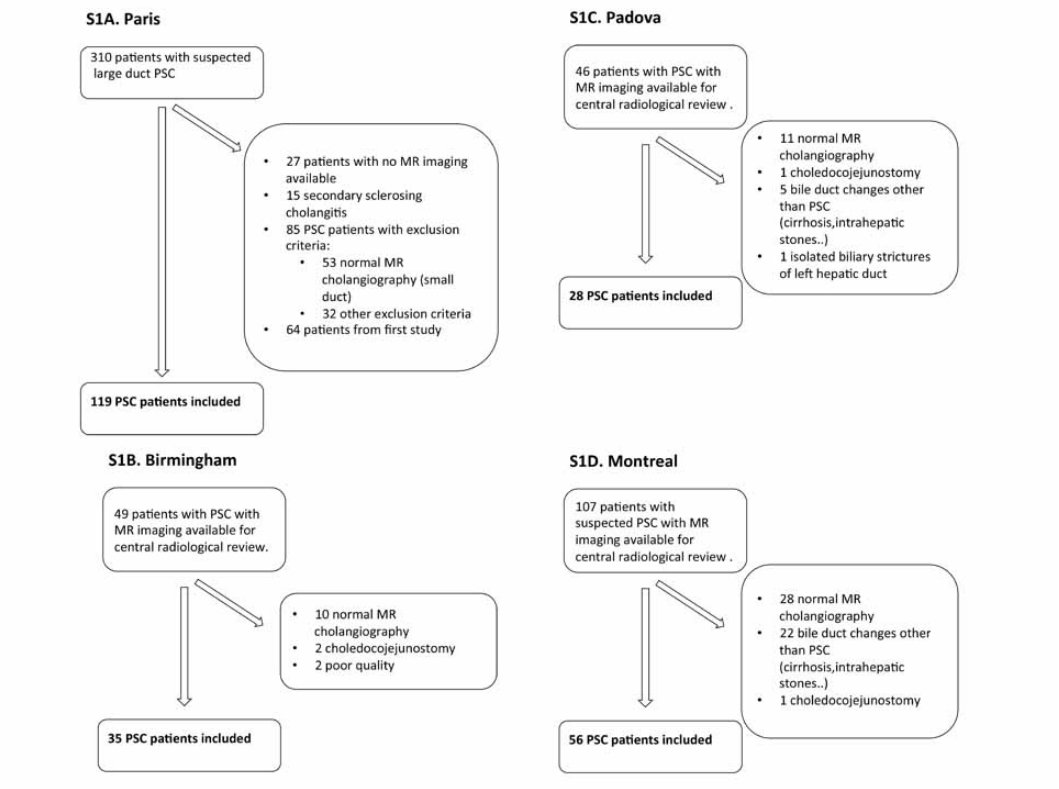
Derivation cohort

Among the 310 PSC patients regularly followed up at Saint-Antoine Hospital in the Reference Centre for Inflammatory Biliary Diseases and Autoimmune Hepatitis, 119 patients were selected according to inclusion and exclusion criteria from the local database to compose the derivation cohort (Supplementary figure 1A). The 64 patients who composed the previous cohort used to build the aforementioned Anali scores [10] were not included.

Validation cohort

The external validation cohort consisted of PSC patients with large ducts PSC regularly followed up at three reference centres for inflammatory biliary disease: the Liver Unit of the Queen Elizabeth Hospital in Birmingham, the Centre for Rare and Cholestatic Liver Disease of the University of Padova and the Liver Unit of the McGill University Health Centre, in Montreal. These patients were selected in each centre according to inclusion and exclusion criteria. Validation cohort patients were not matched to derivation cohort patients. Each MRI available for central reviewing, was reviewed by the two expert radiologists in consensus (LA, SEM) and cases without typical radiological features of large duct PSC were excluded (Supplementary figures 1B, C, D).

Supplementary Figure 1. Flow chart of inclusion in the derivation and validation cohort
Inclusion of patients in the derivation cohort (S1A) and in subgroups of the validation cohort (S1B, S1C, S1D).



MRI Technique

MRI was performed according to the protocol for three dimensional - MRCP previously described [12] and in line with the indications provided by the international PSC study group in the recently published position statement [13]. Pineapple juice (400 mL, 15 minutes before the examination) was used as a negative oral contrast agent. T1-, T2-weighted MR images and three dimensional – MRCP were performed in all cases. When performed, a fat-suppressed T1-weighted ultra-fast gradient-echo acquisition was done 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).

Image analysis

Two abdominal radiologists (LA and SEM with 25 and 12 years of experience in abdominal MRI respectively) reviewed all MRI in consensus. They were blinded to clinical information and course of disease.

Native images and 3D maximum intensity projection reconstructions were analysed on a Workstation, using the Carestream Picture Archiving and Communication System (version 11.32; Carestream Health, Rochester, NY). Maximum intensity projections were analysed on thick slabs of 10 or 20 mm, orientated in the acquisition plane. Cases without typical radiological features of large-duct PSC were excluded.

Analysis of imaging was performed using the standard model already described [10] that included evaluation of:

1. Intrahepatic and extrahepatic biliary ducts with regard to stenosis, dilatation and biliary wall enhancement after contrast injection;
2. Associated liver-related signs including liver parenchymal dysmorphy, heterogeneity of liver enhancement after GBCA injection and portal hypertension;
3. The two Anali scores, without and with gadolinium were assessed:

   Anali without gadolinium = 1 x dilatation of intrahepatic bile duct + 2 x dysmorphy + 1 x portal hypertension (range of possible score: 0-5)

   Anali with gadolinium = 1 x dysmorphy + 1 x parenchymal enhancement heterogeneity (range of possible score: 0-2)

   Intrahepatic bile duct dilatation was scored 0 if ≤ 3 mm, 1 if = to 4 mm and 2 if ≥ 5 mm. Dysmorphy, portal hypertension and parenchymal enhancement heterogeneity were scored 0 if absent and 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 [10].

Clinical data collection

Clinical and biological data were retrospectively collected from patient records in each centre and were reviewed centrally (NC and SL). In both cohorts (derivation and validation), data regarding the date of PSC diagnosis, localization of biliary changes (intra, extrahepatic, intra and extrahepatic) and the association with inflammatory bowel disease were recorded. Biochemical parameters were collected at the time of inclusion (± 3 months), including AST, ALT, ALP, γGT, total serum bilirubin, serum albumin, prothrombin time or international normalized ratio, platelet count. Liver stiffness assessed by transient elastography at the time of inclusion (± 6 months) was also collected when available.

The following clinical events that occurred after inclusion were recorded: acute bacterial cholangitis, hepatobiliary malignancies (including cholangiocarcinoma, gallbladder cancer and hepatocellular carcinoma), endoscopic treatment of biliary strictures, cirrhosis decompensation (ascites development, variceal bleeding, hepatic encephalopathy, persistent bilirubin > 100 µmol/L for more than 3 months), LT, death and cause of death (liver or non-liver related).

Statistical analysis

Patients' characteristics were summarized either as median and interquartile range, or in absolute number and percentages. As assays may vary between hospitals and over time, biochemical variables were expressed as ratio of upper limit of normal.

Continuous variables were compared between the derivation and the validation cohort using Mann-Whitney test. Qualitative variables were compared using chi-square Test or Fisher test as appropriate.

To assess the prognostic value of Anali scores, the endpoint was adverse outcome-free survival. Indeed, data were censored at the date of last visit or the occurrence of adverse outcome, defined as liver-related death, LT or cirrhosis decompensation. In the derivation cohort, we performed univariate Cox regression analysis, using continuous biochemical variables (e.g. AST, ALT, total serum bilirubin, ALP...) and Anali scores, to identify factors associated to the risk of adverse outcome. A receiver-operating characteristics (ROC) analysis including Youden' index calculation was then 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 derivation cohort using Cox backward stepwise regression analysis and then tested in the validation cohort. Two multivariate Cox regression models were separately constructed according to the presence of Anali score without gadolinium in the first model and Anali score with gadolinium in the second model due to 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 v. 23.

RESULTS

General characteristics

We included 238 PSC patients, 119 patients of whom made up the derivation cohort and 119 the validation cohort (28 patients from Padova, 35 from Birmingham and 56 from Montreal). The clinical characteristics of the patients from both cohorts are reported in Table 1. Details of the validation cohort sub-populations are shown in Supplementary Table 1. Overall, 66% of the patients were male and 71% had concomitant inflammatory bowel diseases in both cohorts. Patients from the derivation cohort were younger compared to the validation cohort (36 *vs*. 40 years, respectively, p=0.01). The interval time between the diagnosis of PSC and the inclusion into the study was not significantly different between the two cohorts, with a similar percentage of patients included at the time of PSC diagnosis in the derivation and validation cohorts (52% *vs.* 45%, respectively, N.S.). Biochemical findings at inclusion were similar in the two cohorts of patients, with the exception of higher serum bilirubin levels, and lower platelet count in the validation cohort. Liver stiffness assessed by transient elastography was comparable in the two cohorts.

Table 1. Clinical and biochemical characteristics of PSC patients in the two cohorts.

	Derivation Cohort N = 119	**Validation Cohort N = 119**	**p**
Male gender, n (%)	80(67) *0(0)*	76(64) *0(0)*	N.S.
Age at PSC diagnosis, years	34(21-43) *0(0)*	36(25-51) *0(0)*	0.05
Age at inclusion, years	36(25-50) *0(0)*	40(30-56) *0(0)*	0.01
Interval time between diagnosis and inclusion, years	1(0-4) *0(0)*	2(0-7) *0(0)*	N.S.
Follow-up from inclusion, years	4.4(2.6-6.4) *0(0)*	3.8(1.5-6.2) *0(0)*	N.S.
Patients under UDCA treatment at inclusion	86(72) *33(28)*	54(45) *65(55)*	0.03
Localization at diagnosis: - Intrahepatic only - Intra + extra- hepatic - Extrahepatic only	 32(27) 87(73) 0 *0(0)*	 30(27) 89(75) 0 *0(0)*	N.S.
IBD - Ulcerative colitis - Crohn's disease - Indeterminate	86(72) 51(79) 29(34) 6(7) *0(0)*	85(71) 59(69) 19(23) 7(8) *0(0)*	N.S.
Liver stiffness (KPa)	9 (6.6-12.2) *50(42)*	10.1 (6.0-14.2) *81(68)*	N.S.
Total bilirubin (μmol/L)	15 (10-23) *29(24)*	20(12-33) *20(17)*	0.02
AST (x ULN)	1.3 (0.7-2.7) *21(18)*	1.7(1.0-2.6) *23(19)*	N.S.
ALT (x ULN)	1.6 (0.8-3.2) *21(18)*	1.8(1.1-2.8) *21(18)*	N.S.
γGT (x ULN)	4.1 (1.8-9.7) *19(16)*	4.2(2.5-8.1) *26(22)*	N.S.
ALP (x ULN)	1.6 (0.9-3.0) *19(16)*	1.9(1.1-3.4) *24(20)*	N.S.
Albumin (g/L)	41 (36-44) *40(34)*	36(40-44) *21(18)*	N.S.
Platelets count ($x10^9$/L)	291(199-359) *23(19)*	244(187-290) *21(18)*	0.001

Quantitative variables are expressed as median (interquartile range). Nominal variables are expressed as absolute number (percentage). Missing data are indicated in Italic and expressed as absolute number (percentage). *Abbreviations: UDCA, ursodeoxycholic acid; IBD, inflammatory bowel disease; AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase;* γGT*, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.*

Supplementary table 1. Characteristics of the validation cohort sub-populations.

	Padova Cohort n = 28	**Birmingham Cohort n = 35**	**Montreal Cohort n = 56**
Male gender, n (%)	19 (68) *0(0)*	21 (60) *0(0)*	35 (63) *0(0)*
Age at PSC diagnosis, years	29(20-35) *0(0)*	38(24-55) *0(0)*	41(27-54) *0(0)*
Age at inclusion, years	36(30-43) *0(0)*	46(30-62) *0(0)*	42(28-54) *0(0)*
Localization at diagnosis: - Intrahepatic - Intra + extrahepatic - Extrahepatic	 5 (18) 23 (82) - *0(0)*	 17 (49) 18 (51) - *0(0)*	 8 (14) 48 (86) - *0(0)*
IBD - Ulcerative colitis - Crohn's disease - indeterminate	21 (75) 17 (81) 4(19) - *0(0)*	26 (74) 23 (89) 2 (8) 1 (4) *0(0)*	38 (68) 19 (50) 13 (34) 6 (16) *0(0)*
Liver stiffness (kPa)	8.3(5.4-12.1) *12(43)*	10.9(6.1-16.6) *13(37)*	- *56(100)*
Total bilirubin (μmol/L)	17(8.7-25.5) *0(0)*	20(13-36) *0(0)*	21(13-47) *20(36)*
AST (x ULN)	1.2(0.8-2.0) *1(4)*	1.9(1.1-2.6) *0(0)*	2.2(1.3-3.6) *22(39)*
ALT (x ULN)	1.5(0.7-2.6) *1(4)*	1.8(0.9-2.7) *0(0)*	1.9(1.2-3.5) *20(36)*
γGT (x ULN)	2.8(0.8-6.7) *2(7)*	4.6(2.8-9.3) *0(0)*	5.1(2.9-8.3) *21(38)*
ALP (x ULN)	1.4(0.7-2.1) *1(4)*	3.1(1.6-3.7) *3(9)*	1.9(1.2-3-3) *20(36)*
Albumin (g/L)	41(40-46) *0(0)*	43(38-47) *0(0)*	35(29-40) *21(37)*
Platelets count (x 10^9/L)	250(227-334) *1(4)*	206(143-273) *0(0)*	262(197-304) *20(36)*

Quantitative variables are expressed as median (interquartile range). Nominal variables are expressed as absolute number (percentage). Italic indicates missing data, expressed as absolute numbers (percentage). *Abbreviations: IBD, inflammatory bowel disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase;* γGT*, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.*

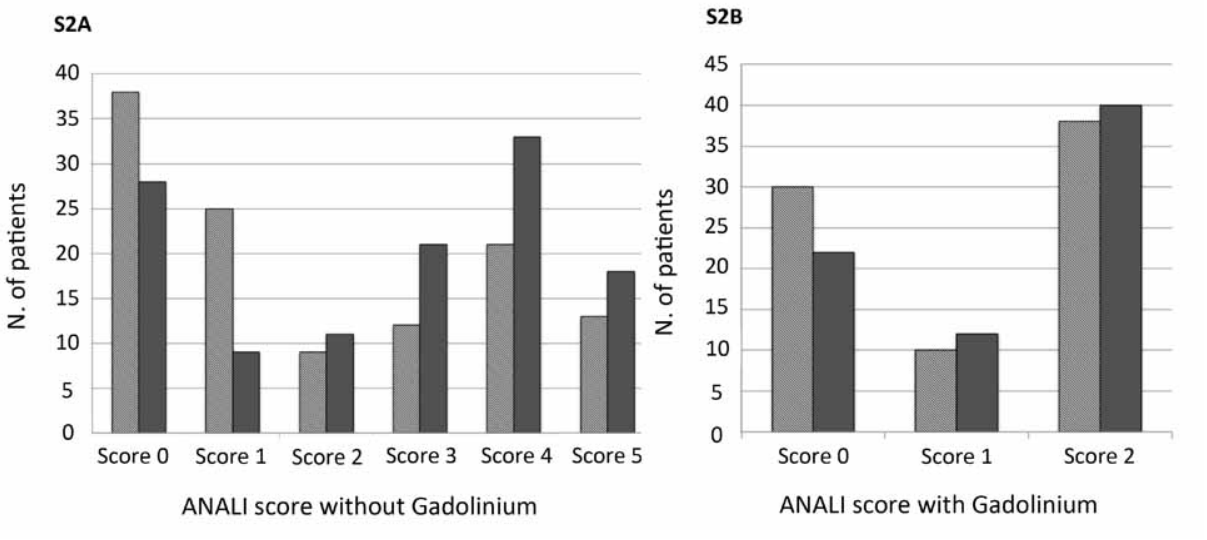
Magnetic resonance descriptive data

MRI with GBCA injection were available in 152 patients: 79 among the derivation (66%) and 73 among the validation cohort (61%). Median Anali score without gadolinium was 1 (0-4) in the derivation cohort, and 3 (1-4) in the validation cohort (p=0.01). Median Anali score with

gadolinium was 1 (0-2) in the derivation cohort, and 2 (0-2) in the validation cohort respectively (N.S.). The distribution of Anali scores is illustrated in Supplementary figure 2.

In the derivation cohort, patients who received GBCA injection had a higher level of serum bilirubin (31 vs. 17 µmol/L, p=0.048) and had 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=0.01). In the validation cohort, no significant clinical, biochemical or radiological difference was observed between subgroups of patients, according to the existence or not of GBCA injection (data not shown).

Supplementary Figure 2. Distribution of patients according to the Anali scores.
Distribution of patients according to Anali score without Gadolinium (S2A) and Anali score with Gadolinium (S2B) in the derivation (light grey bars) and the validation (dark grey bars) cohorts.

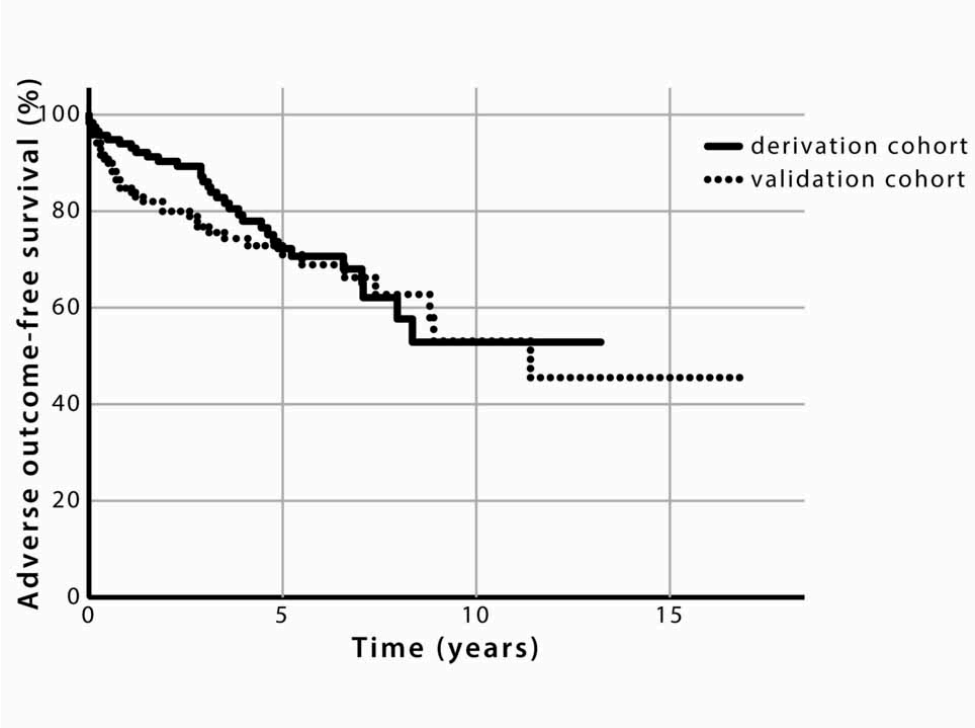


Follow-up and clinical events

In the derivation cohort, a total of 549 patient-years was available. Individual patients were followed up for a median of 4.4 years (2.6-6.4) after inclusion. An adverse outcome as previously defined occurred in 32 patients. During follow-up, eight patients died, seven of whom from liver-related cause: cholangiocarcinoma in five patients, liver failure in one

patient, septic shock of biliary origin in one patient; finally, one myocardial infarction occurred in a patient with decompensated cirrhosis. Twenty patients were transplanted (13 for end-stage liver disease, four for recurrent cholangitis, one for cholangiocarcinoma and two for persistent increased bilirubin serum levels associated with refractory pruritus). Eighteen patients developed decompensated cirrhosis. Seven patients developed colorectal cancer and five patients developed cholangiocarcinoma. Twenty-six (22%) patients experienced at least one episode of acute bacterial cholangitis and 28 received at least one therapeutic ERC. Overall, the 4-year adverse outcome-free survival was 78% ± 4% (Figure 1). In the validation cohort, a total of 497 patient-years was available. Individual patients were followed up for a median of 3.8 years (1.5-6.2) after inclusion. An adverse outcome occurred in 36 patients. During follow-up, five patients died, four of whom from liver-related cause: cholangiocarcinoma in three patients, liver failure in one patient; finally, one urinary bladder adenocarcinoma occurred in one patient with decompensated cirrhosis. Twenty-four patients were transplanted, 18 of whom for end-stage liver disease, two for recurrent bacterial cholangitis, three for persistent increased bilirubin serum levels associated with refractory pruritus, and finally one patient for CCA. Twenty-four patients developed decompensated cirrhosis. Two patients developed CRC, five patients developed CCA and one patient developed hepatocellular carcinoma. Thirty-six (30%) patients experienced at least one episode of acute bacterial cholangitis and 21 underwent at least one therapeutic ERC. Overall, the 4-year adverse outcome-free survival was 73% ± 5% (Figure 1). Overall, the survival without adverse outcome was not significantly different between the derivation and validation cohorts (N.S.) (Figure 1).

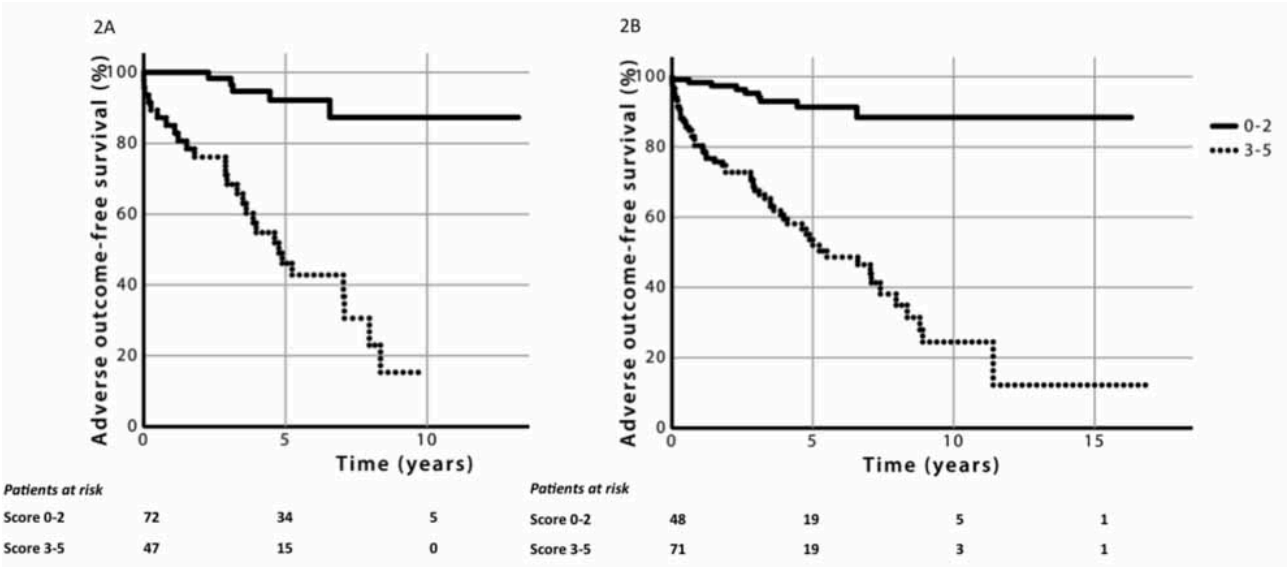
Figure 1. Adverse outcome free-survival in derivation and validation cohorts. Kaplan-Meier curves for adverse outcome-free survival in derivation (solid line) and validation (dashed line) cohorts. Adverse outcome was defined by the occurrence of liver-related death, liver transplantation or cirrhosis decompensation.



Prognostic performance of Anali scores

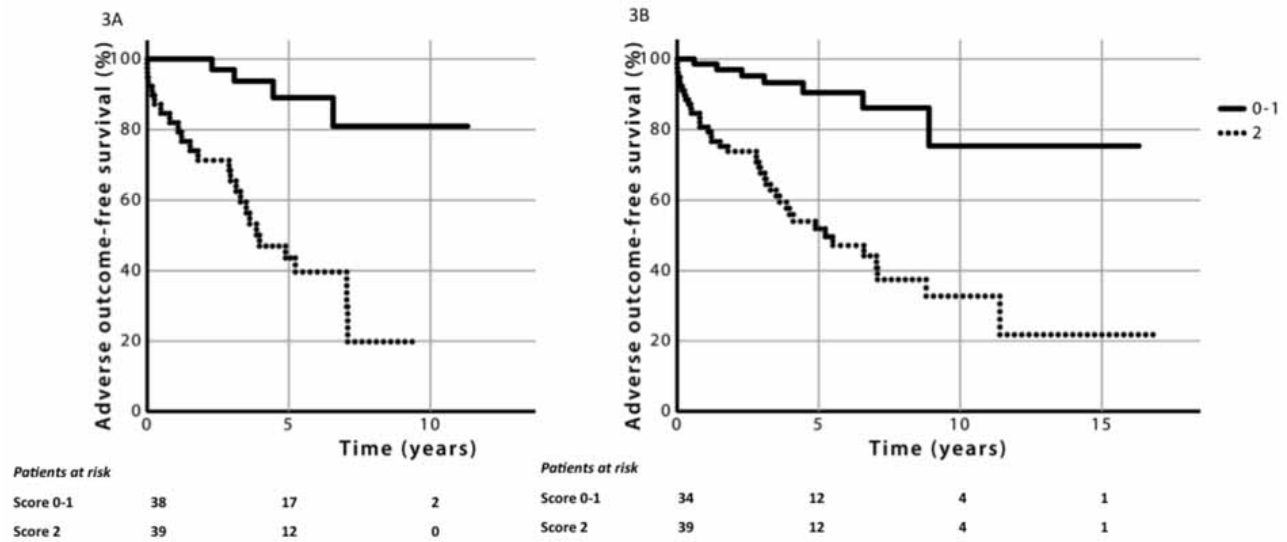
The Anali score without gadolinium was strongly associated with the occurrence of adverse outcome both in the derivation and in the validation cohorts ($p < 0.001$ for both) (Figure 2). In derivation cohort, the area under the receiver operating characteristic curve of Anali score without gadolinium was 0.89 [$IC_{95\%}$0.84-0.95]). The cut-off value with the highest total sensitivity and specificity was 2 (sensitivity, 84%; specificity, 77%; positive predictive value, 57%; negative predictive value, 93%).

Figure 2. Adverse outcome free-survival according to Anali score without gadolinium. Kaplan-Meier curves for adverse outcome-free survival in derivation (2A) and validation (2B) cohorts, according to Anali score without gadolinium. The solid line represents patients with Anali score without gadolinium ≤2 and the dashed line represents patients with Anali score without gadolinium >2.



The Anali score with gadolinium was also strongly associated with the occurrence of adverse outcome in both derivation and validation cohorts (p=0.001 and p=0.003, respectively) (Figure 3).

Figure 3. Adverse outcome-free survival according to Anali score with gadolinium. Kaplan-Meier curves for adverse outcome-free survival in derivation (3A) and validation (3B) cohorts, according to Anali score with gadolinium. The solid line represents patients with Anali score with gadolinium ≤1 and the dashed line represents patients with Anali score with gadolinium >1.



In derivation cohort, area under the receiver operating characteristic curve of Anali score with gadolinium was 0.76 $IC_{95\%}$ [0.64-0.87]. The cut-off value with the highest total sensitivity and specificity was 1 (sensitivity, 85%; specificity, 68%, positive predictive value 59%, negative predictive value 89%).

Likewise, in the validation cohort, area under the receiver operating characteristic curve of Anali scores without and with gadolinium were 0.76 $IC_{95\%}$ [0.67-0.85] and 0.73 $IC_{95\%}$ [0.61-0.85], respectively.

In the derivation cohort, the prognostic values of Anali scores without and with gadolinium were analysed with those of biochemical variables significantly associated with adverse outcome-free survival at univariate analysis, namely AST, ALT, γGT, ALP, total bilirubin, and albumin (Table 2).

Table 2. Features associated with adverse outcome-free survival in the univariate analysis in the derivation cohort.

Parameter	Log-Rank	p
Total serum bilirubin > 17 µmol/L	19.8	<0.001
AST > 1.7 x ULN	22.6	<0.001
ALT > 1.6 x ULN	4.8	0.028
γGT > 5 x ULN	11.3	0.001
ALP > 2 x ULN	11.1	0.001
Albumin < 36 g/L	10.3	0.001
ANALI without gadolinium > 2	36.3	<0.001
ANALI with gadolinium > 1	19.9	<0.001

Abbreviations: AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase; γGT*, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.*

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).

Table 3. Features associated with adverse outcome-free survival in the multivariate analysis (Cox regression model 1 including Anali without gadolinium) in the derivation cohort.

Parameter	HR	95% CI	p
Anali without gadolinium > 2	24.948	3.25-191.75	0.002
Total bilirubin > 17 µmol/L	3.823	1.26-11.62	0.018

Abbreviations: HR, hazard ratio; CI, confidence interval.

In the second Cox regression model, including Anali score with gadolinium, the radiological score was the only independent predictor of adverse outcome-free survival; a trend of significance was also observed for alkaline phosphatase (Table 4). In this model total bilirubin was excluded because the model did not converge due to the presence of a significant correlation between total bilirubin and Anali score with gadolinium ($r = 0.467$, $p < 0.001$).

Table 4. Features associated with adverse outcome-free survival on multivariate analysis (Cox regression model 2 including Anali with gadolinium) in the derivation cohort.

Parameter	HR	95% CI	p
Anali with gadolinium > 1	13.72	1.76-107.03	0.012
ALP > 2 x ULN	3.068	0.85-11.02	0.086

Abbreviations: HR, hazard ratio; CI, confidence interval; ALP, alkaline phosphatase; ULN, upper limit of normal

In the validation cohort, Cox regression model confirmed that Anali score without gadolinium was independently associated with adverse outcome-free survival (Hazard Ratio 3.56, 95% confidence interval 1.206 – 10.475, $p = 0.021$). A trend was also observed for total bilirubin in the same model (Hazard Ratio 2.36, 95% confidence interval 0.94-5.97, $p = 0.069$). As well, Anali score with gadolinium was independently associated with adverse outcome-free survival in the validation cohort (Hazard ratio 5.27, 95% confidence interval 1.54-18.01, $p= 0.008$).

DISCUSSION

The aim of this study was to assess the clinical prognostic value of two simple MR risk scores (with and without gadolinium), that, as we previously showed, were able to predict radiologic progression [10]. MRCP is the recommended modality for the diagnosis of PSC [9] and in addition, recent data have suggested that hepatobiliary cancer surveillance (including MR imaging) in PSC patients improved the outcome and survival [14], possibly expanding the clinical utility of a regular MRI to follow-up evaluation.

As a consequence, it seems crucial to test the prognostic value of MR features. Besides the non-invasive nature of MR, another advantage of these two MR risk scores is that they combine both cholangiographic changes (presence and severity of intrahepatic biliary dilatation) and the consequences of biliary disease on the liver parenchyma (dysmorphy, portal hypertension and heterogeneity of parenchymal enhancement after GBCA injection) thus allowing a global evaluation of the impact of the disease on the liver.

Our results show that, by using two large derivation and validation cohorts including 238 patients with large-duct PSC, these two scores were independently associated with the occurrence of adverse outcome, suggesting that the radiologic progression in PSC patients is predictive of adverse clinical outcome. Here, we demonstrate that Anali scores have significant prognostic value in patients with PSC. Indeed, in the derivation cohort, the risk of developing an adverse outcome on patients with high Anali scores without and with gadolinium, is 25- and 13-fold higher, respectively than in patients with low Anali scores. Moreover, the prognostic performance of the two radiologic scores exceeds those of validated biochemical markers (ALP, bilirubin). The prognostic values of these two scores have been confirmed in the validation cohort.

Reports on the prognostic value of MR features in PSC patients are scarce. In a retrospective study including 53 patients, Kitzing *et al.* found that progressive hepatic morphologic changes on serial MR imaging were associated with adverse clinical outcome [15] but the authors did not report on biliary abnormalities. Other studies have reported that arterial [16] and delayed [17] peribiliary enhancement were associated with a higher Mayo risk score whereas Tenca *et al*. found only a weak correlation between MR cholangiography score for extra-hepatic bile ducts and hard end-points (death and LT) [18]. Finally, taking advantage of the large phase 2 Simtuzumab trial (NCT01672853), Muir *et al.* proposed a MR imaging risk score based on MR cholangiography findings at baseline [19]. This score, based on portal hypertension, dysmorphy and enlarged perihepatic nodes, was associated with the development of clinical events. However, the follow-up was limited to two years and in contrast with our study, the authors included all PSC related-events as, *i.e.* mostly ascending cholangitis (57% of clinical events) and jaundice (27%) with a low percentage of cirrhosis decompensation (13%) [19].

In the current study, the population used to evaluate the prognostic value of the two Anali scores was composed by half of patients included at PSC diagnosis and the other half after diagnosis, with a wide interval time between diagnosis and inclusion. Therefore, the prognostic value of these two Anali scores has been assessed at different time points in different patients thus expanding the clinical applicability of these scores. Nevertheless, radiological interpretation of MRI remains a challenge in PSC patients, as recently pointed out by Zenouzi *et al.* [20]. In order to decrease the subjectivity of MRCP interpretation, we herein applied a standard model of interpretation [20] and the two Anali scores were calculated using binomial variables (dysmorphy, portal hypertension and heterogeneity of liver parenchyma after gadolinium injection) and a categorical variable (intrahepatic biliary dilatation) resulting

in two simple and easy-to-calculate scores. Yet, the inter-observer variability of Anali scores will be specifically addressed in future studies that will include non-expert radiologists.

Several patients from the different groups were excluded because the two expert reviewers did not find any significant abnormality at MRCP. We assume that such exclusion may strengthen the results of the present study as, by nature, inclusion of patients with normal MRCP, which are 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 [13]. As a result, the local policy in Saint-Antoine centre is to perform GBCA injection according to the radiologist judgement of the disease severity and this explains why injected patients in the derivation cohort presented a more severe disease as confirmed by higher bilirubin and higher Anali score without gadolinium compared to non-injected patients. This, together with the smaller sample size, could at least in part explain the lower prognostic performance of Anali score with gadolinium compared to Anali score without gadolinium. A connection between gadolinium injection and abnormal signal within dentate nucleus and the globus pallidus has been recently demonstrated [21,22] and brain abnormal signal has been more frequently observed with the use of hepatospecific GBCA [23] . Children and young adults with PSC are candidate to have repeated MRI and may be at higher risk of gadolinium retention in the brain. Because of the good prognostic performance of Anali score without gadolinium, we recommend to perform MRI with gadolinium only if a hepatobiliary cancer is suspected. Diffusion-weighted imaging has a

growing interest in PSC imaging [13,24] and might replace the need for GBCA injection to evaluate liver parenchymal heterogeneity provided that its diagnostic performance is validated.

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

This study has some limitations: it is a retrospective study with its intrinsic bias and missing data, intra-observer and inter-observer variabilities of the two MR scores were not assessed and the Anali scores were evaluated only at a single time point, precluding to determine the prognostic value of dynamic changes of the scores in subsequent MRI. Moreover, comparison with other validated prognostic scores or liver stiffness was not performed. Therefore, further studies should address these issues and especially assess the prognostic performance of Anali scores in combination with liver stiffness.

However, this work has also major strengths including the study of two wide cohorts of well characterized PSC patients with pure large ducts PSC, excluding overlap syndrome and hepatic comorbidities that would have modified both radiologic features and outcome, the adequate follow-up, the choice of hard and objective endpoints and finally, the central radiological reviewing by two expert radiologists.

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

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CHAPTER 7

Magnetic resonance risk score and liver stiffness by transient elastography have complementary prognostic values in patients with primary sclerosing cholangitis

Nora Cazzagon

ABSTRACT

Background and aims

MR risk score, (Anali score without gadolinium) and LS were previously associated with clinical outcomes in PSC patients. The aim of the current study was to assess the complementary values of Anali score and LS in assessing prognosis of PSC patients.

Patients and methods

Patients with PSC from three European centers (Paris, Birmingham and Padova) with a 3D-MRCP available for central revaluation and a valid LS assessed by Fibroscan (Echosens, Paris) performed within 6-months interval or less were included in a longitudinal retrospective study. Exclusion criteria consisted of decompensated cirrhosis, primary liver cancer, acute cholangitis, PSC-autoimmune hepatitis variant and small duct PSC. All MRI were reviewed by two radiologist and the Anali score was calculated: Anali score= (1 x dilatation of intrahepatic bile ducts) + (2 x dysmorphy) + (1 x portal hypertension). The primary endpoint was survival without LT or cirrhosis decompensation. The prognostic value of LS and Anali score were assessed using Cox proportional hazard models. Optimal cutoffs were defined by the Youden's index. Survival rate were assessed using the Kaplan Meier method.

Results

162 patients (60% men; median age 37 years; 78% IBD) were included. A total of 753 patient-years was available. Forty patients experienced an adverse outcome (4 LT, 6 liver-related death and 30 cirrhosis decompensations). LS and Anali score were significantly correlated (ρ=0.51, p<0.001) and individually associated with clinical outcomes (p<0.001 for both). Optimal prognostic thresholds were 10.5 KPa for LS and 2 for Anali score (Hazard Ratios: 2.07, p=0.03 and 3.78, p=0.001, respectively). The frequency of adverse outcomes according to LS and Anali score was 8.3% (LS $\leq$ 10.5 kPa and Anali $\leq$ 2), 24%(LS > 10.5 kPa or Anali >2

separately) and 55% (LS > 10.5 kPa and Anali >2), respectively (p=0.001). A significant difference in mean survival of these 3 subgroups of patients was observed (Log-Rank 26.8, p<0.001).

Conclusion

Combination of MRI and Fibroscan improves the stratification of PSC patients into different risk groups for adverse outcomes.

INTRODUCTION

PSC is a rare chronic cholestatic disease affecting intra and/or extrahepatic biliary tree and characterized by the presence of strictures and dilatations of bile ducts[1]. Different disease subtypes have been associated with different prognosis [2]. Large duct PSC is the most typical presentation of PSC and is characterized by the presence of alternating strictures and dilatations of intra- and/or extrahepatic bile ducts. Radiological progression over time was reported in 20-58% of patients[3,4]. Moreover, the disease might evolve towards progressive fibrosis, cirrhosis and its complication. The evolution is variable among different patients and in the last 30 years different prognostic models based on invasive and non-invasive assessment have been proposed but none is recommended in individual patient[5]. Liver stiffness (LS) assessed by Fibroscan is a useful, non-invasive measure of the histological stage[6–8] in PSC. Moreover, LS and LS changes over time were associated to adverse outcome free survival in different cohorts of PSC patients[7,8]. MRI is the first modality recommended for the diagnosis of PSC[5,9] . In Chapter 6 we reported, in a large multicentric retrospective cohort of pure large duct PSC patients, that two simple magnetic resonance risk scores, called Anali scores without and with Gadolinium and the increased total bilirubin, were independently associated to adverse outcome free survival. It is unknown whether the use in combination of these two non-invasive techniques could better stratify PSC patients with different risks of developing adverse outcomes. Thus, the aim of our study was to assess whether LS and MR risk score have complementary prognostic value.

PATIENTS AND METHODS

We designed a longitudinal retrospective study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the protocol was approved by the Ethic Committee or the Institutional Review Board of all participating centers. Informed consent in writing was obtained by each patient according to the local ethic committee policy. Inclusion criteria were: age at inclusion ≥ 18 years, diagnosis of large duct PSC, one liver MRI with MRCP available for analysis and a valid LS assessed by transient elastography performed within 6 months from MRCP, at least one year of follow-up after the inclusion. The date of inclusion was defined as the date of the closest MRCP to PSC diagnosis available for analysis. Exclusion criteria were: small duct PSC, PSC-autoimmune hepatitis variant, previous LT or presence of concomitant hepatic morbidities (viral or non-viral hepatitis and secondary sclerosing cholangitis), decompensated cirrhosis or primary liver cancer, acute bacterial cholangitis or any relevant comorbidities associated with short-term poor prognosis at the time of inclusion.

Study population

Patients were recruited at the Reference Centre for Inflammatory Biliary Diseases and Autoimmune Hepatitis of Saint Antoine Hospital in Paris, at the Liver Unit of the Queen Elizabeth Hospital in Birmingham and at the Centre for Rare and Cholestatic Liver Disease of the University of Padova. Patients were selected, according inclusion and exclusion criteria, among the cohort of PSC patients of our previous study (Chapter 6). Moreover, by applying the same criteria, we included additional patients from Paris selected among the 64 patients which composed the original cohort used to derived the two MR risk scores [4].

MRI Technique

MRI was performed according to the protocol for 3D-MRCP previously described [10] and in line with the indications provided in the position statement of the International PSC study group[11]. Pineapple juice (400 mL, 15 minutes before the examination) was used as a negative oral contrast agent. T1-, T2-weighted MRI and 3D-MRCP were performed in all cases. When performed, a 3D fat-suppressed T1-weighted ultra-fast gradient-echo acquisition was done before and after intravenous administration of 20 mL of gadolinium-based contrast agent (GBCA) with hepatic arterial, portal venous, and equilibrium phase acquisition (30 s, 80 s, and 3 min, respectively).

Image analysis

Two abdominal radiologists (LA and SEM with 25 and 12 years of experience in abdominal MRI respectively) reviewed all MRI in consensus. They were blinded to clinical information and course of disease. Native images and 3D maximum intensity projection (MIP) reconstructions were analysed on a Workstation, using the Carestream Picture Archiving and Communication System (version 11.32; Carestream Health, Rochester, NY). MIPs were analysed on thick slabs of 10 or 20 mm, orientated in the acquisition plane. Analysis of imaging was performed using the standard model already described [4] and the MR risk score without GBCA injection, Anali score without gadolinium was calculated according to the formula:

Anali score without gadolinium = 1 x dilatation IHBD + 2 x dysmorphy + 1 x portal hypertension

Intrahepatic bile duct dilatation was scored 0 if dilation ≤ 3 mm, 1 if equal to 4 mm and 2 if ≥ 5 mm. Dysmorphy and portal hypertension were score 0 if absent and 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[4].

Clinical data collection

Clinical and biological data were retrospectively collected from patient records in each centre and were centrally reviewed. LS assessed by TE performed within 6 months from the date of inclusion was collected. TE was performed using the M probe of Fibroscan (Echosens, Paris, France). Only procedures with 10 valid measurements, a success rate of at least 60%, and an interquartile range/median ratio lower than 30% were considered eligible for inclusion. Moreover, data regarding the date of PSC diagnosis, localization of biliary changes (intra, extrahepatic, intra and extrahepatic) and the association to inflammatory bowel disease (IBD) were recorded. Biochemical parameters were collected at time of inclusion (± 3 months) including AST, ALT, ALP, γGT, total bilirubin, albumin, prothrombin time or INR, platelet count. The following clinical events that occurred after inclusion were recorded: cirrhotic decompensation (ascites development, variceal bleeding, hepatic encephalopathy, persistent bilirubin > 100 μmol/L for more than 3 months), hepatobiliary malignancies, LT), death and cause of death (liver or non-liver related).

Statistical Analysis

Patient characteristics were summarized either as median and interquartile range (IQR), or in percentages. Biochemical variables were expressed as ratio of upper limit of normal (x ULN) since assays may vary between hospitals and over time. To assess the prognostic value of Anali score without gadolinium and of the liver stiffness, the composite endpoint was adverse outcome-free survival. Indeed, follow-up was censored at the date of last visit or occurrence of an adverse outcome, defined as liver-related death, LT or cirrhotic decompensation. The individual prognostic values of LS and Anali score without gadolinium were assessed by

performing univariate Cox regression model using LS and Anali score as continuous variables. Then, a logistic c-statistic analysis was applied to determine the optimal threshold of Anali score without gadolinium and liver stiffness that best predicted the occurrence of adverse outcome. Harrel's c-statistic was also applied. Moreover, Cox backward stepwise regression analysis in order to assess the prognostic value of Anali score without gadolinium and LS and their weight on the rates of survival was performed after dichotomization of the two variables according the cut-off identified at ROC analysis. Survival rates were calculated based on the Kaplan-Meier estimates and Log-rank test analysis was applied to assess whether survival was different between subgroups of patients having a different number of prognostic factors. Group 1 was defined by the presence of both LS and Anali score lower than the respective cut offs, group 2 was defined by the presence of at least one of the two variables higher than the cut off and group 3 was defined by the presence of both factors higher than the cut off. All analyses were carried out using Statistical Package for the Social Sciences, SPSS, (ver 24.0). P-values <0.05 were considered significant.

RESULTS

General characteristics

We included 162 patients, of them 124 were followed-up in Paris, 22 in Birmingham and 16 in Padova. Characteristics of patients are reported in table 1. Seventy percent of patients were males, with a median age at diagnosis and at inclusion of 35 and 37 years respectively. A concomitant IBD was diagnosed in 78% of patients and in most of cases it was represented by ulcerative colitis. The median delay between diagnosis and inclusion was 2 years. PSC was localized in intra- and extrahepatic bile ducts in 69% of patients and in intrahepatic ducts only in the rest of the population. Median total bilirubin was normal. Median liver stiffness was 8.8 KPa (6.6-12.3). Distribution of patients according to the Anali score is reported in table 1.

Table 1. Clinical and biochemical characteristics of cohort of PSC patients.

Characteristics	**PSC population (n=162)**
Male gender	111(69) *0(0)*
Age at PSC diagnosis, years	35(22-44) *0(0)*
Age at inclusion, years	37(28-51) *0(0)*
Interval time between diagnosis and inclusion, years	2(1-6) *0(0)*
PSC localization: - Intrahepatic - Intra + extra- hepatic - Extrahepatic	*0(0)* 51(31) 111(69) -
IBD, n (%) - UC - CD - indeterminate	126(78) *0(0)* 77(61) 42(33) 7(6)
Liver stiffness (KPa)	8.8(6.6-12.3) *0(0)*
Total bilirubin (μmol/L)	15(10-21) *9(5)*
AST (x ULN)	1.2(0.7-2.3) *9(5)*
γGT (x ULN)	3.4(1.2-6.6) *9(5)*
ALP (x ULN)	1.5(0.8-2.8) *11(7)*
Albumin (g/L)	42(39-45) *21(13)*
Platelets (x10^9/L)	269(202-334) *7(4)*
Anali score without gadolinium 0 1 2 3 4 5	 35(22) 28(17) 26(16) 23(14) 35(22) 15(9)

Quantitative variables are expressed as median (interquartile range). Nominal variables are expressed as absolute number (percentage). Italic indicates missing data within the cohort and are expressed as absolute number (percentage). *Abbreviations: IBD, inflammatory bowel disease; LS, liver stiffness; AST, aspartate aminotransferase; γGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.*

Correlation between liver stiffness, Anali score without gadolinium and biochemical variables

Anali score without gadolinium and liver stiffness positively correlated ($\rho = 0.51$, $p < 0.001$). Liver stiffness positively correlated with total bilirubin, AST, ALP, GGT and negatively correlated with albumin and platelets count (Table 2). Finally, Anali score without gadolinium positively correlated with total bilirubin, AST, ALP, GGT and negatively correlated with albumin (Table2).

Table 2. Correlation between liver stiffness and Anali score without gadolinium and biochemical variables.

	Liver Stiffness		**Anali score without gadolinium**	
	Spearman's ρ	**P**	**Spearman's ρ**	**P**
Total bilirubin	0.35	<0.001	0.24	0.003
AST	0.52	<0.001	0.34	<0.001
ALP	0.48	<0.001	0.33	<0.001
GGT	0.50	<0.001	0.40	<0.001
Albumin	-0.31	<0.001	-0.26	0.0022
Platelets	-0.18	<0.001	-0.09	n.s.

Abbreviations: AST, aspartate aminotransferase; γGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.

We also analysed the distribution of dysmorphy and degree of intrahepatic bile duct dilatation according the different groups of LS according to previously reported cut off corresponding to different METAVIR stages (F0-F1<8.5 kPa, F2 8.6-9.5 kPa, F3 9.6-14.3 kPa, F4 ≥14.4 kPa) [7] (Figure 1 and Figure 2). As expected, the frequencies of dysmorphy and high grade of intrahepatic bile duct dilatation were higher in patients with LSM corresponding to severe fibrosis or cirrhosis (LSM > 9.5 KPa) (Figure 1 and 2). On the other hand, presence of dysmorphy was documented also in early stage of fibrosis (Figure 1).

Figure 1. Distribution of dysmorphy assessed by MRI in different stages of fibrosis assessed by Fibroscan.

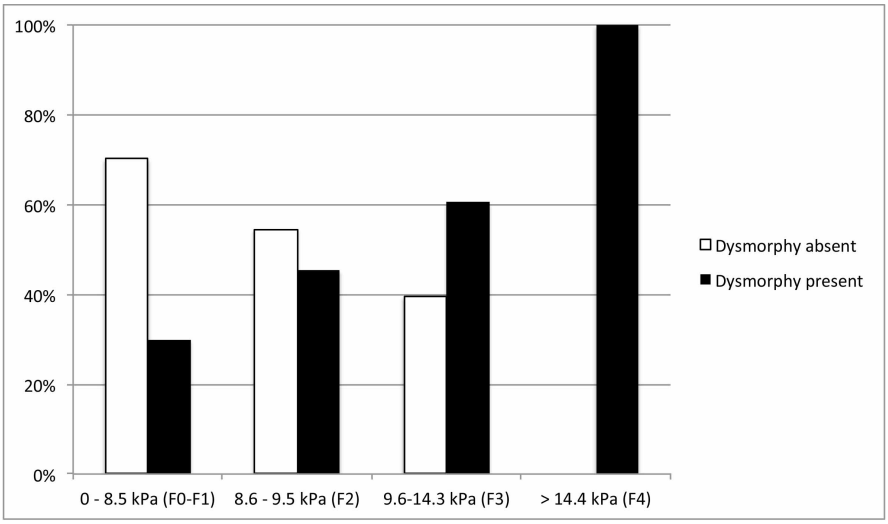
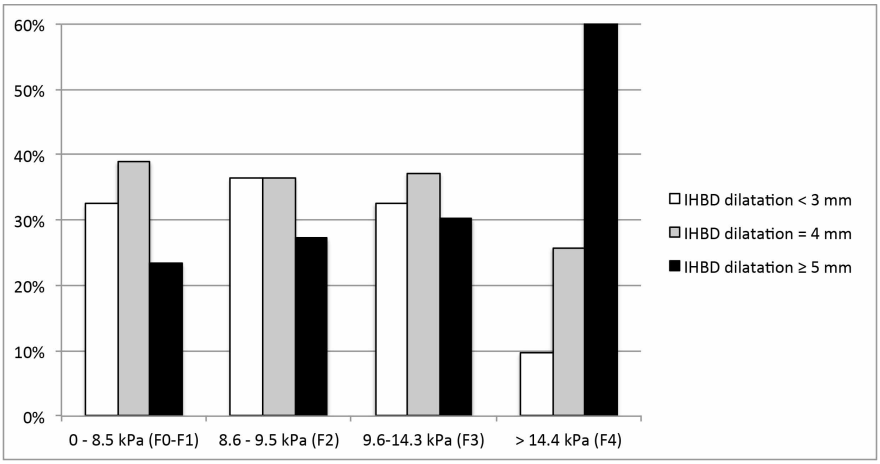


Figure 2. Distribution of different grades of intrahepatic bile duct dilatation in different stages of fibrosis assessed by Fibroscan.



Follow-up and clinical events

A total of 753 patient-years was available in the entire cohort. Among the 162 patients, 40 patients (25%) experienced at least one adverse outcome in an average of 4.5 ± 4.3 years after inclusion. The adverse outcomes included: four liver transplantations (all for end-stage liver disease), six liver-related deaths (five from cholangiocarcinoma and one from acute cholangitis complicated by septic shock) and thirty cirrhosis decompensations.

Prognostic performance of Anali score without gadolinium and liver stiffness

By univariate analysis, both Anali score without gadolinium and liver stiffness were strongly associated with the occurrence of adverse outcome (p<0.001 for both) (Table 2, Figures 2-3).

Table 2. Univariate analysis of parameters associated with adverse outcome-free survival.

Parameter	OR	95% CI	p
Liver stiffness	1.037	1.021-1.054	**<0.001**
Anali score without gadolinium	1.918	1.501-2.451	**<0.001**

Logistic c-statistic for LS measurement was 0.71 (0.61-0.80). Harrel's c-statistic for LS was 0.68. The cut off value for LS with the highest total sensitivity and specificity was 10.5 kPa (Sensitivity, 60%; Specificity 73%; Positive Predictive Value 42%, Negative Predictive Value 85%). Logistic c-statistic for Anali score without gadolinium was 0.82 (0.76-0.89). Harrel's c-statistics for Anali score without gadolinium was 0.76. The cut off value for Anali score without gadolinium with the highest total sensitivity and specificity was 2 (Sensitivity 80%, Specificity 66%, Positive Predictive Value 44%, Negative Predictive Value 91%. The associated hazard ratios, found at Cox regression analysis, were 3.78 (95% CI 1.67-8.59, p=0.001) for ANALI score without gadolinium > 2 and 2.07 (95% CI 1.06-4.06), p=0.03) for liver stiffness > 10.5 KPa.

Figure 3. Adverse outcome-free survival according to liver stiffness. Kaplan-Meier curves for adverse outcome-free survival according to liver stiffness. The solid line represents patients with liver stiffness ≤10.5 KPa and the dashed line represents patients with liver stiffness > 10.5 KPa.

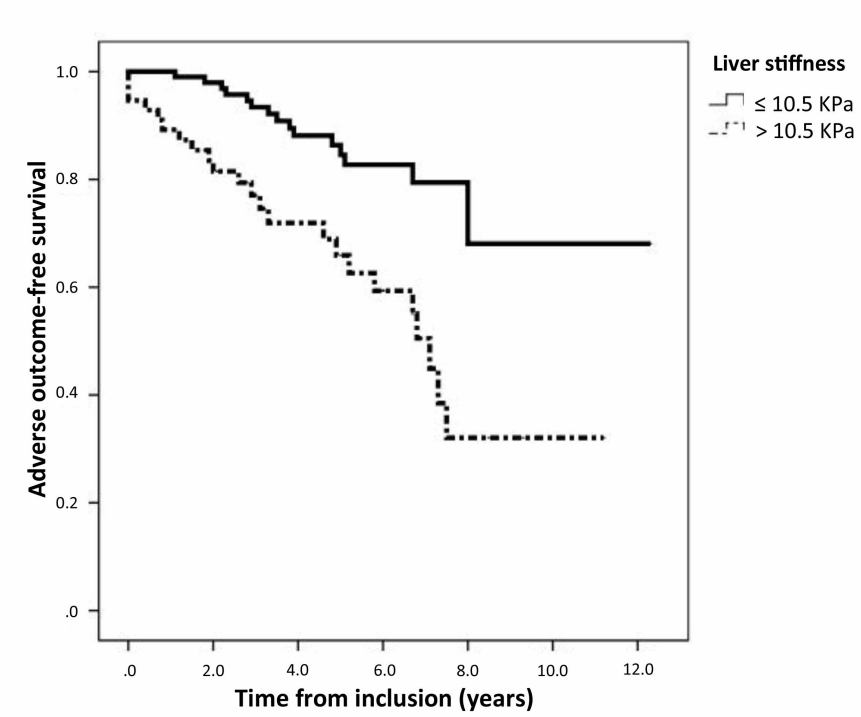
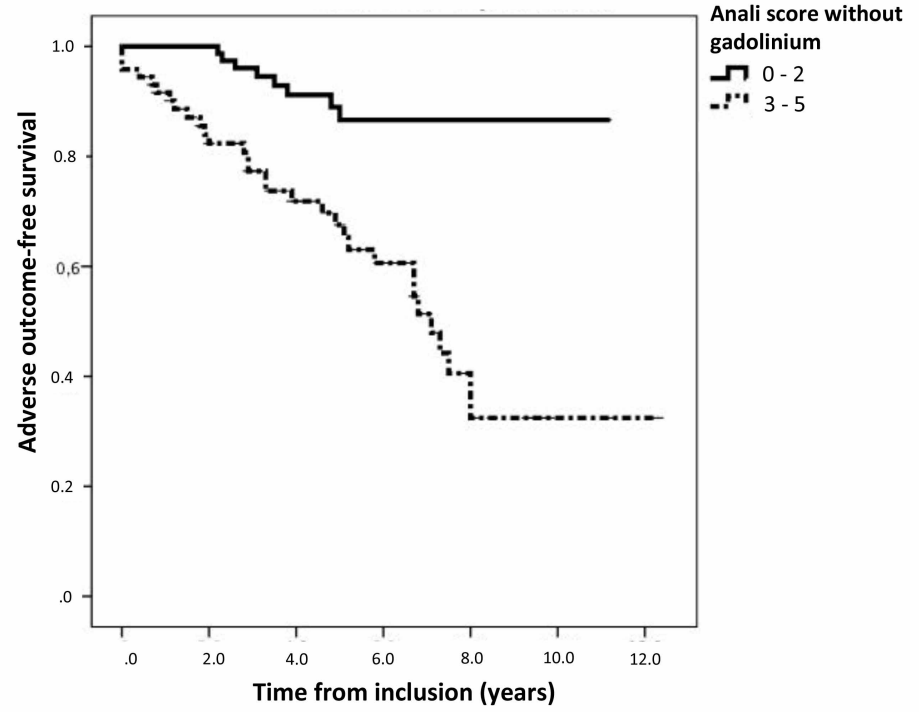


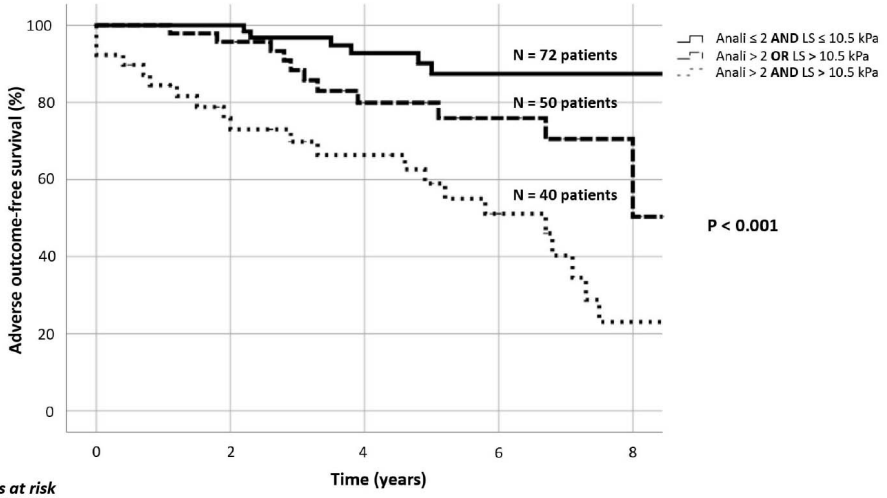
Figure 4. Adverse outcome-free survival according to Anali score without gadolinium. Kaplan-Meier curves for adverse outcome-free according to Anali score without gadolinium. The solid line represents patients with Anali score without gadolinium ≤2 and the dashed line represents patients with Anali score without gadolinium >2.



Use in combination of LS and Anali score without gadolinium

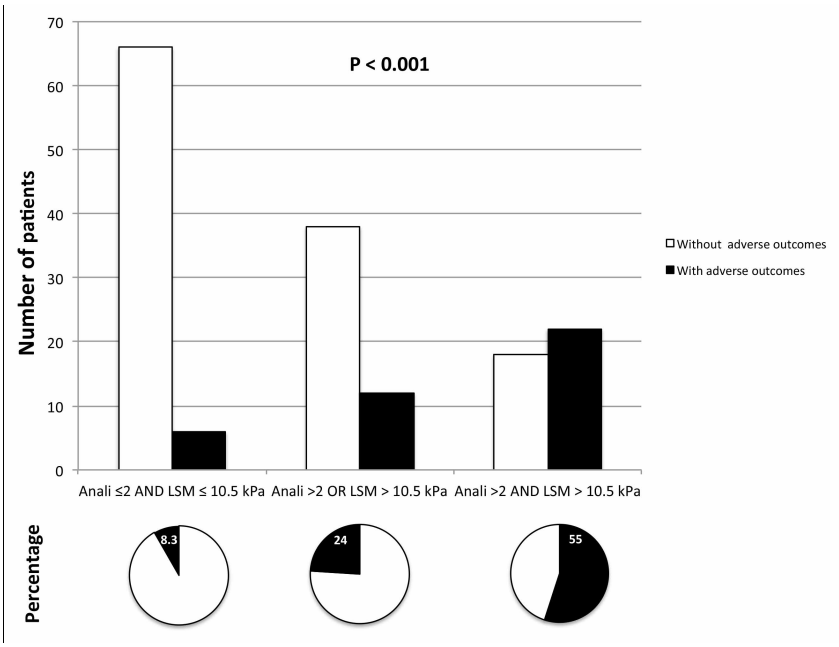
Subgrouping patients according to the presence of LS and Anali score without gadolinium above or below the identified cut off we identified three subgroups of patients. Group 1 included 72 patients (44%) characterized by both Anali score without gadolinium ≤ 2 and LS ≤ 10.5 KPa, group 2 included 50 patients (31%) characterized by Anali score without gadolinium > 2 or LS > 10.5 KPa and finally group 3 included 40 patients (25%) characterized by both Anali score without gadolinium and LS above the respective cut off. Survival analysis shows a significant difference between the mean survivals of patients included in the three subgroups (Log rank 26.8, p < 0.001) (Figure 5) with a corresponding hazard ratio of 2.7 (95% CI, 1.78-4.12, p<0.001). Moreover, the percentage of patients with adverse outcomes in the three groups differs significantly (8.3% in group 1, 24% in group 2 and 55% in group 3, p < 0.001) (Figure 6). C-statistic for the use in combination of LS and Anali score without gadolinium was 0.78.

Figure 5. Kaplan-Meier curves for adverse outcome-free according to Anali score without gadolinium. The solid line represents patients with Anali score without gadolinium ≤2 and LS ≤ 10.5 KPa, the dotted line represents patients with Anali score without gadolinium > 2 or LS > 10.5 kPa and the dashed line represents patients with Anali score without gadolinium > 2 and LS > 10.5 kPa.



Patients at risk					
Anali ≤ 2 **AND** LS ≤ 10.5 kPa	72	64	42	21	7
Anali > 2 **OR** LS > 10.5 kPa	50	42	24	16	6
Anali > 2 **AND** LS > 10.5 kPa	40	25	19	11	4

Figure 6. Distribution of clinical events according different cut off value of Anali score without gadolinium and LSM.



DISCUSSION

In this study we evaluated the use in combination of LS and a simple MR score to evaluate prognosis in patients with PSC and we reported their complementary value. First, we analysed the prognostic value of the single parameters. LS demonstrated a prognostic performance similar to that previously reported in a French cohort [7] and a in combined German-French cohort [8] of PSC patients . The optimal cut-off for LS in current study was 10.5 kPa and it was comparable to that observed in pure large ducts PSC of the French study[7] (11.1 kPa) and in the German-French cohort[8] (12.4 kPa). Moreover, the recent results of Simtuzumab trial reported a similar c-statistic for LS at baseline for predicting PSC clinical events in. In the latter, an optimal cutoff of 8.5 kPa at baseline was able to discriminate patients with different risk to develop clinical events (acute cholangitis, cirrhosis decompensation and CCA)[12]. This cutoff was lower than that we observed and this is reasonably due to the inclusion of acute

cholangitis within the clinical events, but these events are not correlated with the histological stage as opposed to cirrhosis decompensation.

Second, Anali score without gadolinium demonstrated a similar prognostic performance to that reported in our previous study. This, is, at least in part, due to the inclusion of two third of patients of our previous cohort (**Chapter 6**). On other hand, we here included 48 French patients which were originally part of the cohort used to derive the two MR risk score [4]. This justifies the longer follow-up (753 patients-years) in the current compared with the previous study (549 and 497 patient-years in derivation and validation cohort, respectively) (**Chapter 6**). This observation confirmed the prognostic value of Anali score without gadolinium also in patients with an extended follow-up.

Here, we confirmed that LS and Anali score without gadolinium are significantly correlated and moreover they are both correlated with disease activity and severity as documented by the correlation with biochemical variables. Moreover, by Cox regression model both Anali score without gadolinium and LS were independently associated with adverse outcome free survival and, when used in combination, we distinguished three subgroups of patients with significantly different mean survival. The risk to develop adverse outcome was increased of 170 times by adding one risk factor (HR 2.7, 95% CI, 1.78-4.12, $p<0.001$).

As we stated, the primary aim of our study was to assess the use in combination of these two techniques, rather than their comparison, since they described different phases of the disease. Liver stiffness thanks to its continuous assessment of liver elasticity is able to differentiate between different histological stages[6–8]. In other hand, Anali score without gadolinium combines three morphological findings characterizing the disease and independently associated with radiological progression[4]. Indeed, Anali score without gadolinium takes into account three pathophysiological aspect of the disease. First, it

evaluates the severity of biliary disease, by assessing the degree of dilatation of intrahepatic bile ducts; second, it evaluates the impact of biliary damage obstruction on liver parenchyma by assessing dysmorphy and finally, it describes the extrahepatic impact of the disease by evaluating the presence of portal hypertension. The latter represents an expression of advanced disease and when present it strongly impact on prognosis. On the other hand, we here reported that dysmorphy was clearly more frequent in patients with LS corresponding to severe fibrosis and cirrhosis, but, more interesting, dysmorphy was also present in patients with LS corresponding to minimal/moderate fibrosis. This confirms that in PSC, dysmorphy is not an unequivocal feature of cirrhotic stage but it also represents the presence of focal atrophy of liver parenchyma[13,14]. Finally, the frequency of large intrahepatic bile duct dilatation was higher in patients with advanced fibrosis and cirrhosis and thus confirms that the severity of intrahepatic bile duct disease is correlated with advanced fibrosis and a worst prognosis[15,16].

The distribution of the single component of Anali score without gadolinium according the different LS intervals, representing different histological stages according METAVIR, here reported, confirms that this MR risk score is not only able to discriminate between presence and absence of cirrhosis. The value of each incremental point of Anali score without gadolinium, alone and in combination with different interval of LS, in stratifying patients at different risks of developing adverse outcome might be addressed in a larger cohort of PSC patients.

In this study we excluded the previously proposed MR score after GBCA injection, which is based on the presence of dysmorphy and the assessment of heterogeneity of parenchymal enhancement after GBCA injection. This choice was due to the reduced availability of MRI with GBCA injection in this population that it would have significantly reduced the sample size.

Moreover, as reported in our previous study, the administration of GBCA, at Saint-Antoine Hospital, is performed according radiologist judgement of the disease severity. Thus, using Anali score with gadolinium would have implied also the inclusion of a more homogenous cohort of PSC patients with advanced disease.

Despite the retrospective nature, this study has some major strengths, including a large cohort of well characterized PSC patient, one fifth followed-up in two others European centers, the central revaluation of radiological and clinical data for each patient and the adequate follow-up from inclusion in the study.

In conclusion, this multicentric international study demonstrates the complementary prognostic value of the MR risk score without gadolinium and liver stiffness. Their combination ameliorates the prediction of risk of adverse outcome and it enhances the risk stratification of patients thus providing a useful tool to improve the selection of patients for future clinical trials.

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CHAPTER 8

Intrahepatic cystic biliary dilatation constitutes a significant prognostic factor in patients with primary sclerosing cholangitis

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Eur Radiol 2018 Aug 29, DOI 10.1007/s00330-018-5697-3

ABSTRACT

Aims To evaluate the prognostic value of cystic dilatation (CD) of the intrahepatic biliary ducts in patients with PSC.

Methods A single-center cohort of 205 patients with PSC from 2003 to 2016 was analyzed. CD was defined by quantitative and qualitative criteria. Radiological and clinical courses were assessed. A Kaplan-Meier analysis was used to estimate cumulative survival without liver transplantation (LT) from the date of PSC diagnosis. A log-rank test was performed to compare survival time of PSC patients with and without CD.

Results A total of 15 (7.3%) PSC patients (12 males) with a median age of 23 years at diagnosis had CD. Five patients had one CD; seven patients had two or three CDs; and three patients had diffuse CD. CDs ranged in small diameter size from 12 to 32mm. Radiological evolution of CD was markedly variable. However, a radiological worsening of PSC over time was observed in all patients. The clinical course was characterized by the occurrence of complications in most patients. Half of the patients with CD underwent LT at a median time of 40 months from diagnosis of CD and the median survival time from PSC diagnosis was significantly lower than in PSC without CD (10.7 vs. 23.4 years; HR 3.8, 95% confidence interval: 1.7–8.3, p = 0.001).

Conclusions CD in PSC is an unusual condition that mostly affects young patients. It is characterized by a rapid, unfavorable course and constitutes a significant prognostic factor.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare, heterogeneous, chronic cholestatic liver disease characterized by inflammation and fibrosis of the biliary tree [1,2]. Magnetic resonance cholangiography (MRC) is recommended as the first-line non-invasive imaging method for patients with suspected PSC [3–6]. The primary MR cholangiography features of PSC include multifocal intra- and extrahepatic bile duct stenosis alternating with slightly dilated ducts, but these findings are markedly variable and probably related to the stage of the disease process and its pattern [7]. In contrast with other causes of biliary obstruction such as tumours, biliary dilatations in PSC are usually mild to moderate and when a marked dilatation is present a cholangiocarcinoma complicating PSC should be excluded [6–8].

In our Institution, the policy of the management of PSC includes a routine yearly MRI/three-dimensional (3D)-MRC. In this annual follow-up, we regularly observed an uncommon form of PSC characterized by cystic dilatation (CD) of intrahepatic ducts not related to a downstream biliary stenosis. Only sporadic cases of CD of biliary ducts in PSC have been reported in the literature [9–14]. Moreover, the clinical significance and the prognostic value of this particular disease's presentation have not yet been assessed.

The goal of the present study was to determine the prognostic value of CD in PSC.

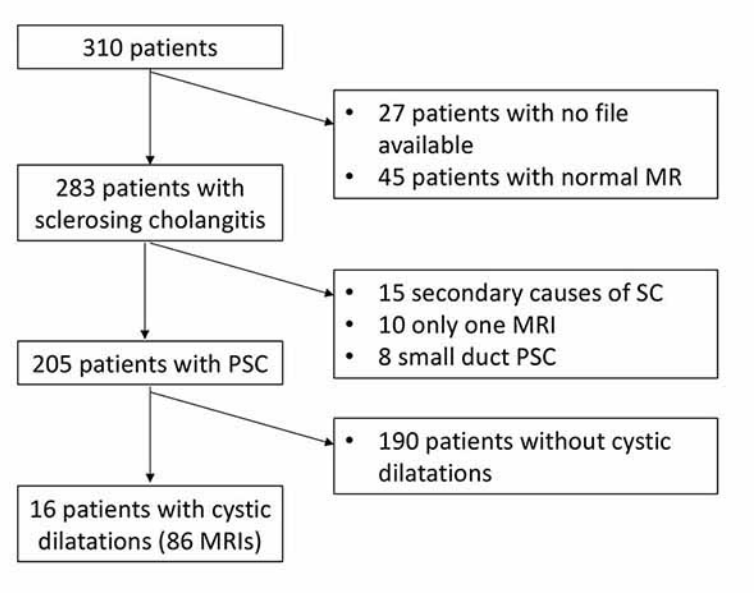
PATIENTS AND METHODS

Study population

Radiologic files from a series of 310 consecutive patients with PSC were retrospectively reviewed. MRCs were performed between 2003 (implementation of 3D-MRC in our centre)

and April 2016 (date of inclusion termination). Diagnosis of PSC in these patients was based on the aforementioned criteria[3–5]. Patients who underwent at least two 3D-MRCs with at least a 1-year interval were included in the study. Exclusion criteria were normal MRC, secondary sclerosing cholangitis, cystic fibrosis, patients with only one MRC and small-duct PSC as shown in the flow chart (Figure 1).

Figure 1. Patients suspected to have primary sclerosing cholangitis



Cystic dilatation of the intrahepatic biliary ducts was defined by a marked dilatation of the intrahepatic biliary ducts measuring at least 10 mm of small diameter with biconvex contours (loss of parallelism of biliary duct edges), not related to a downstream biliary stricture. Connection of CDs with intrahepatic ducts was confirmed by analysis of thin source images. This value of 10 mm corresponds to the double of a previously described major dilatation of the intrahepatic bile ducts (≥ 5 mm) [15] and was the threshold used by Harrison and Hubscher in a previous study [16].

Our faculty hospital's Institutional Review Board approved the review of radiological and clinical data for this study. Informed consent was waived for this retrospective study.

MRC technique

MRI was performed according to the protocol for 3D-MRC previously described by our group and in line with the indications given by the international PSC study group in the recently published position statement[17,18]. T1-, T2-weighted MR images and 3D-MRC were performed in all cases. When performed, a 3D fat-suppressed T1-weighted ultra-fast gradient-echo acquisition was done before and after intravenous administration of 20 ml of Gd-DOTA (Dotarem, Guerbet, Aulnay-sous-Bois, France), with hepatic arterial portal venous and equilibrium phase acquisition (30 s, 80 s and 3 min, respectively).

Data analysis

Two radiologists (with 25 and 12 years, respectively, of experience in abdominal imaging) reviewed all MRCs in consensus. The criteria of image analysis included the following:

MRC features of cystic biliary dilatation

- Number of CDs (only one CD [group 1], two or three CDs [group 2], and more than three CDs [group 3]), location, and maximum size
- Presence of calculi within CD
- Contrast enhancement of wall of dilated biliary ducts
- Evolution of CD over each MRC during patient follow-up.

The "reference MRC" has been defined as the MRC in which the maximum diameter of the CD was present to define a time point that has been used to analyse clinical data.

MRC features of PSC

We analysed the first available MRC and the reference MRC (MRC with maximal diameter of CD) with regard to an interpretation standard model already described [15].

This standard model of interpretation includes analysis of the following:

- Intrahepatic and extrahepatic biliary ducts with regard to stenosis, dilatation and biliary wall enhancement.
- Associated liver-related signs including dysmorphy, heterogeneity of liver enhancement after contrast injection and portal hypertension.
- Two MRI progression risk scores (i.e. 'Anali scores) [7]without and with gadolinium were assessed on the first available MRC [MRI progression risk score (without gadolinium) = 1 × dilatation IHBD + 2 × dysmorphy + 1 × portal hypertension and MRI progression risk score (with gadolinium) = 1 × dysmorphy + 1 × parenchymal enhancement heterogeneity].

Clinical characteristics

Information from the medical files was reviewed by an independent hepatologist (with 10 years of experience in hepatology). The following data were collected:

- Clinical presentation of the disease at diagnosis and at reference MRC (symptoms and laboratory values)
- Therapy started before the development of CD (especially type and length of immunosuppressive therapy)
- Clinical evolution of these patients over time: status, development of complications of disease. We considered April 2017, 1 year after the end of inclusion date, to be the end of the follow-up period.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation, median (range) or number (%). Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Quantitative variables were compared using the chi-square test or Fisher's exact test when appropriate. The median follow-up of patients was calculated from the diagnosis of PSC to the last follow-up. Kaplan-Meier's survival analysis was performed to estimate cumulative survival from the date of PSC diagnosis. Median survival times of patients with and without CD were calculated for death or liver transplant. The statistical comparison between survival of patients with and without CD and the calculation of the hazard ratio of death or liver transplant were performed using the log-rank test [19]. Statistical analysis was performed using IBM SPSS Statistics 24.

RESULTS

Study population

After reviewing the MRCs of the 310 patients, 205 patients were found to have a typical radiological pattern of PSC. 105 patients were excluded because of a normal MRC, availability of only one MRC or diagnosis of secondary sclerosing cholangitis or small duct PSC as shown in the flow chart (Fig. 1). Finally, 15 of 205 (7.3%) patients were found to have CD-PSC. Clinical features at the time of diagnosis in PSC patients with and without CD are presented in Table 1. The 15 patients with CD were primarily male (n=12), with a young age at diagnosis of PSC (range 14–43 years, median 23 years) and at reference MRC (range 19–63 years, median 29 years). The median follow-up time from PSC diagnosis to the last follow-up date was 8 years (range 3–28 years). A total of 86 MRCs were obtained in these 15 patients (two to ten MRCs

for each patient). Eleven (73%) patients developed an inflammatory bowel disease (IBD) before (n=7), at (n=2) or following (n=2) diagnosis of PSC. PSC patients with CD were younger, had higher levels of bilirubin, alkaline phosphatase and aspartate aminotransferase, and more frequently had an intra and extrahepatic localization than did PSC patients without CD (Table 1).

Table 1. Clinical characteristics of PSC patients with and without CD at the time of PSC diagnosis.

	PSC patients with CD (n.15)	**PSC patients without CD (n.190)**	**P**
Male gender	12 (80%)	122 (64%)	NS
Age at PSC diagnosis (yrs)	25 ± 10	35 ± 15	**0.013**
Radiological localization - Intrahepatic only - Extrahepatic only - Intra-extrahepatic	 - - 15 (100%)	 85 (50%) 4(2%) 82 (48%)	**0.001**
Overlap syndrome with autoimmune hepatits (PSC-AIH)	2 (13%)	17 (9%)	NS
IBD	11(73%)	130/190 (68%)	NS
Histological stage III-IV (advanced fibrosis - cirrhosis) at diagnosis	4/9 (44%)	21/106 (20%)	NS
Total bilirubin (µmol/L)	38.3 ± 27.0	25.7 ± 48.7	**0.047**
ALP (× ULN)	3.2 ± 1.7	1.8 ± 1.4	**0.016**
AST (× ULN)	3.8 ± 2.3	1.8 ± 1.7	**0.004**
Albumin (g/L)	39.4 ± 5.7	41.1 ± 5.7	NS
Platelets (*10^9/L)	278 ± 67	297 ± 120	NS

Continuous variables are expressed as mean ± standard deviation.
Abbreviations: AP, alkaline phosphatase; AST, aspartate aminotransferase; ULN, upper limit of normal; IBD, inflammatory bowel disease.

MRC features of CD

Five patients had a single CD (group 1); seven patients had two or three CDs (group 2); and three patients had diffuse CDs (group 3) (Table 2; Figs. 2, 3 and 4). Connection of CDs with intrahepatic biliary ducts was confirmed by analysis of source images in all cases. All CDs had biconvex contours. CDs were hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images and on MRC images. Maximum CD was located within the left

intrahepatic biliary ducts in eight patients, the right intra hepatic biliary ducts in six patients, and within the caudate lobe in one patient. CDs of the intrahepatic biliary ducts ranged between 12 and 32 mm (mean, 19mm). Calculi were observed within the CD in 12 patients. Calculi were hyperintense on T1- and hypointense on T2- and MRC images in all cases. On the other hand, calculi were not observed within non-dilated biliary ducts (Figs. 2 and 4). In one patient, contrast injection was not performed. In the other 14 patients, contrast enhancement of the CD wall was observed in 13 patients. Contrast enhancement was observed at the arterial phase in ten patients and at portal and equilibrium phases in all 13 patients (Table 2, Fig. 3). During follow-up, the evolution of CD was markedly variable.

CDs were present at the first available MRC in seven patients. In the other eight patients, CD appeared during follow-up. There was an improvement over time for eight patients, including a complete disappearance of CD in four patients. In two patients, CD worsened during follow-up. In four patients, CD was fluctuant with alternation of worsening and improvement (Fig. 4). CD was stable in only one patient (Table 2). With regard to MRC features of CD, we did not observe any significant difference between the three groups.

Table 2. MRC features of cystic dilatation and PSC.

Patient	Sex	Age	Group	CD Size (mm)	Calculi	Contrast enhancement	CD on first MRI	Evolution	Anali without	Anali with
1	M	19	1	12	+	+	+	I	3	1
2	M	42	1	13	+	+	-	S	4	I
3	M	63	1	12	+	-	+	F	5	NA
4	F	23	1	19	+	NA	+	I	4	2
5	F	24	1	29	+	+	-	W	5	2
6	M	24	2	32	+	+	+	I	5	2
7	M	25	2	30	+	+	-	I	4	2
8	M	39	2	21	-	+	-	I	2	NA
9	M	29	2	16	+	+	+	I	5	2
10	M	20	2	20	+	+	+	I	2	1
11	M	21	2	12	+	+	-	I	0	NA
12	M	40	2	14	-	+	-	W	0	NA
13	M	33	3	24	+	+	+	F	4	2
14	M	38	3	16	-	+	-	F	1	NA
15	F	30	3	17	+	+	-	F	2	NA

Abbreviations: CD, cystic dilatation, NA, not applicable; I, improvement; S, stability; W, worsening; F, fluctuation.

Figure 2. A 24-year-old woman with a single cystic biliary dilatation.

Magnetic resonance cholangiography (MRC) performed 48 months before reference MRC (a) demonstrates severe stenosis of main biliary duct (black arrow) and severe and diffuse stenosis of intrahepatic biliary ducts (white arrows). Reference MRC (b) demonstrates a long severe stenosis of main biliary duct with dilatation of main biliary duct above (black arrow). Single cystic dilatation (CD) of left intrahepatic biliary duct (C) is demonstrated. Perihepatic ascites (A) is also demonstrated. Corresponding T2- (c) and T1-weighted MR images (d) demonstrate calculi (arrows) within cystic (C) dilatation.

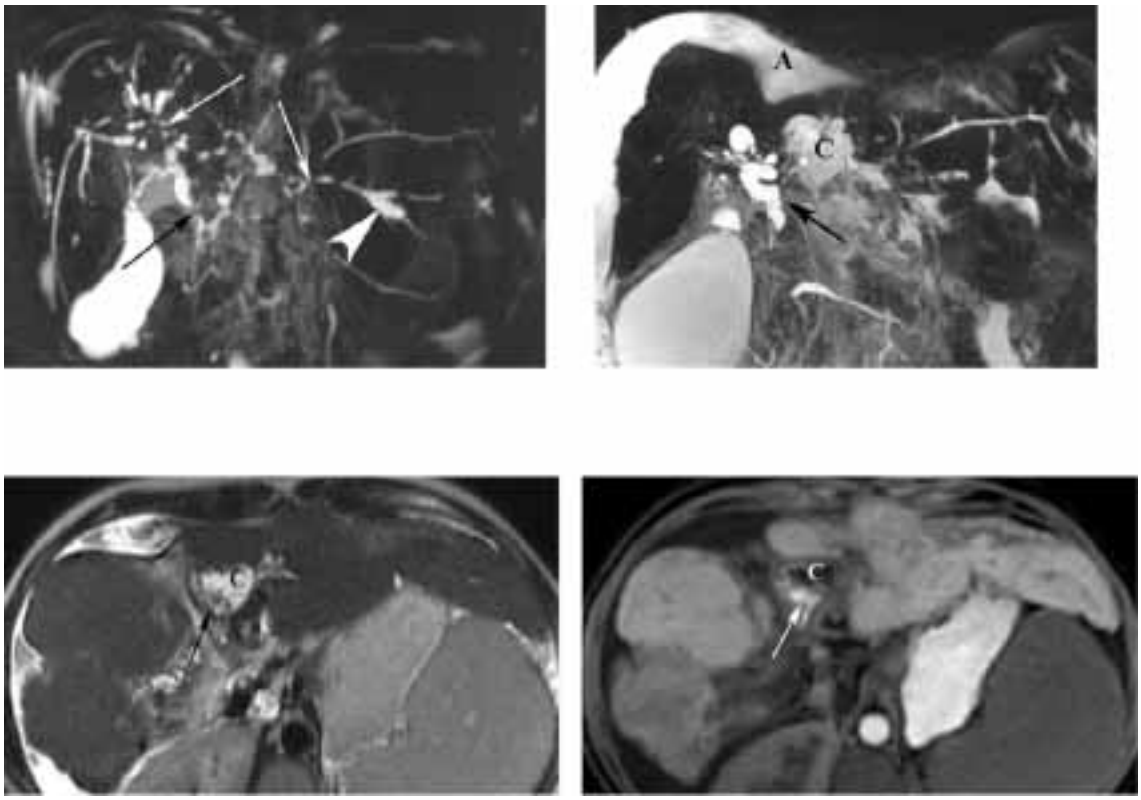


Figure 3. A 40-year-old man with two cystic biliary dilatations.

MRC performed 24 months before reference MRC (a) demonstrates mild stenosis of main biliary duct (arrow) and severe stenosis of intrahepatic biliary ducts (thin arrows). Dilatation of intrahepatic biliary ducts (arrowhead) is also demonstrated. Reference MRC (b) demonstrates two cystic biliary dilatations within left lobe of liver (arrowheads). Contrast enhanced T1-weighted MR image (c) in transverse plane demonstrates wall enhancement of cystic dilatation and of right biliary duct (arrows). MRC performed 60 months after reference MRC (d) demonstrates diffuse severe stenosis of intrahepatic biliary ducts with dilatation of intrahepatic biliary ducts (arrows). Cystic dilatation of left intrahepatic biliary duct (arrowhead) has markedly decreased.

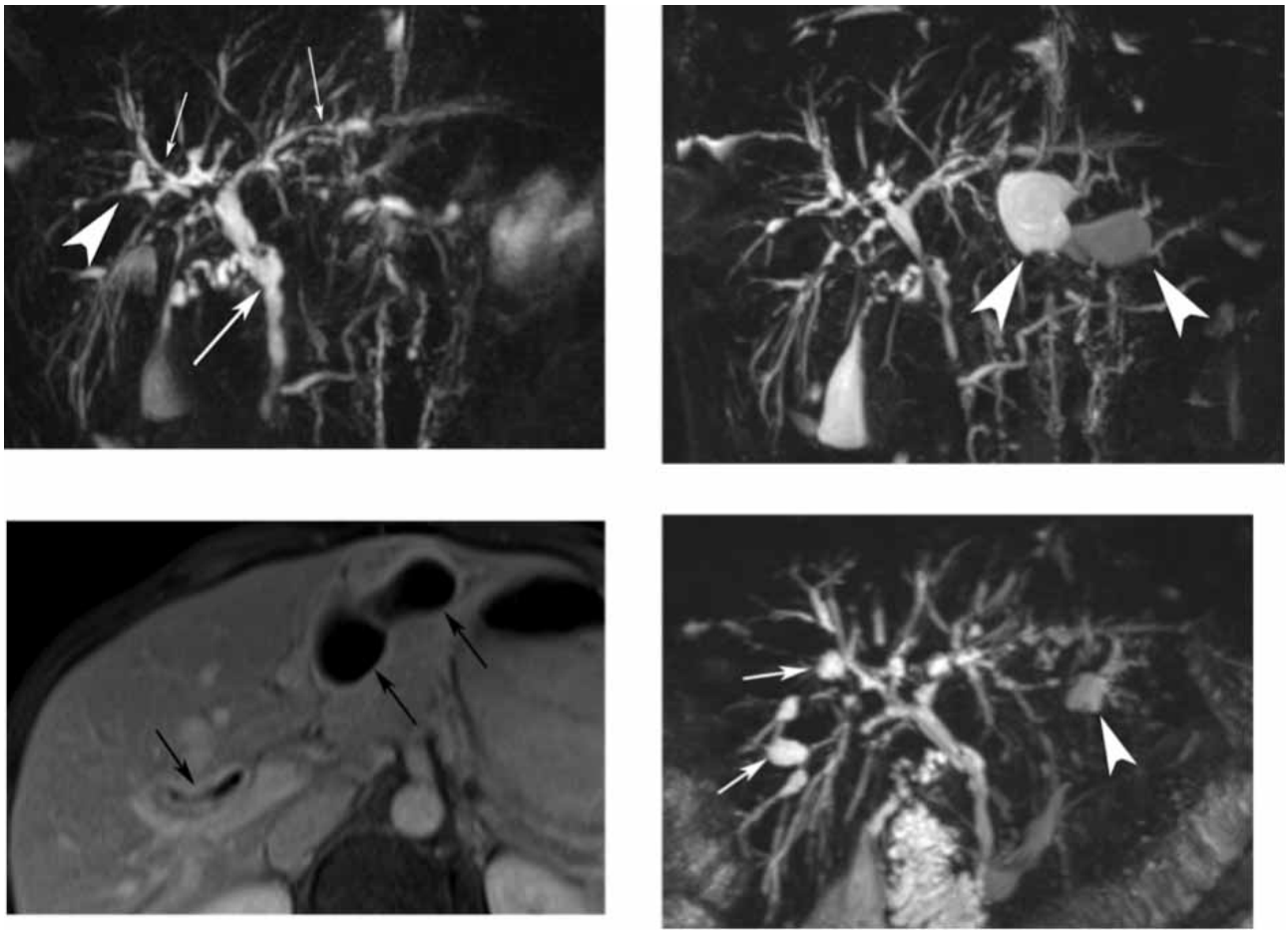
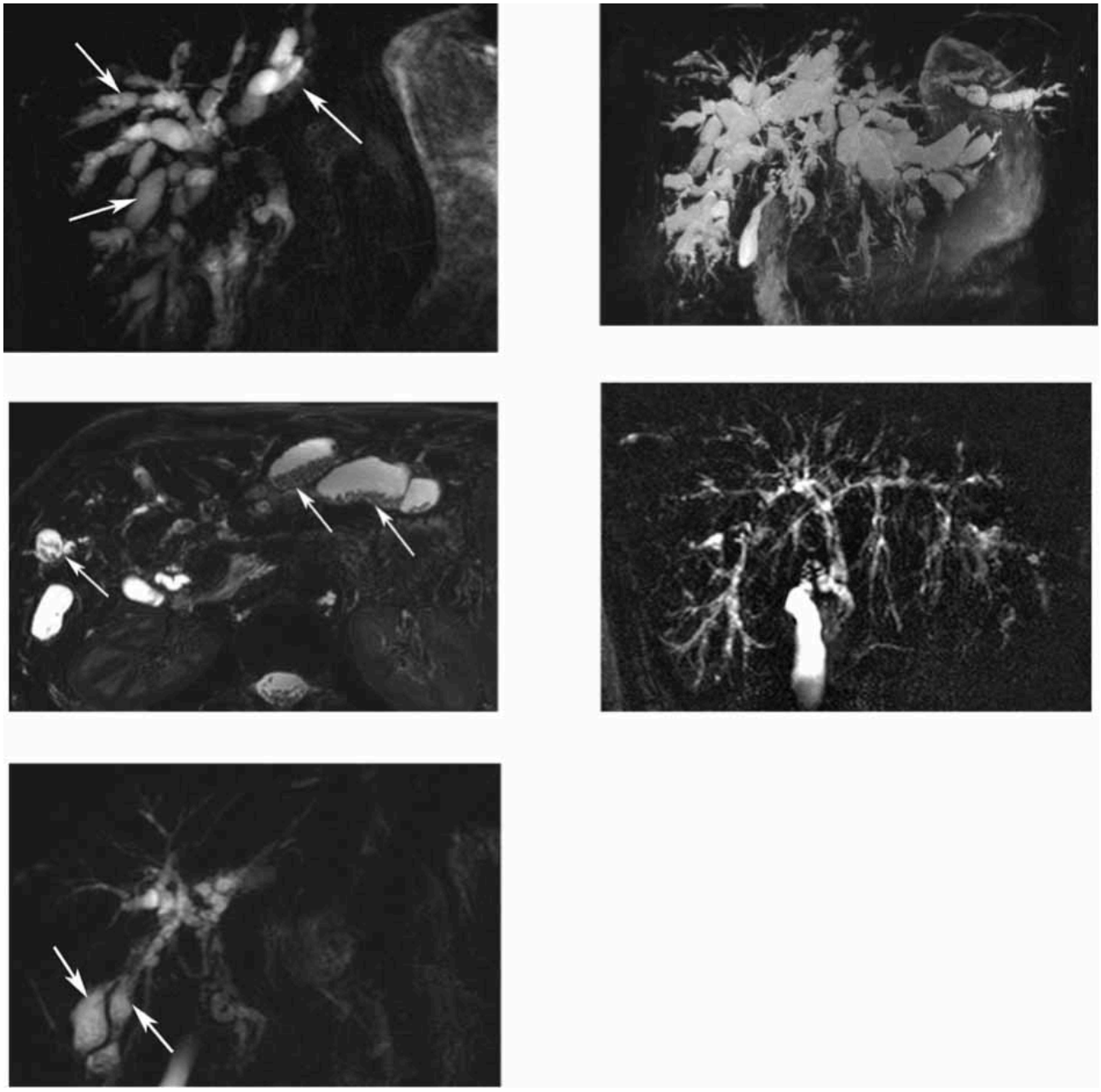


Figure 4. A 33 year-old-man with diffuse cystic biliary dilatation.

MRC performed 3 months before reference MRC (a) demonstrates diffuse and severe stenosis of intrahepatic biliary ducts with dilatation of intrahepatic biliary ducts (arrows). Reference MRC (b) demonstrates diffuse cystic biliary dilatation. 20 mm Maximum Intensity Projection reconstructed image in the transverse plan (c) demonstrates multiple calculi (arrows) within dilated biliary ducts. MRC performed 12 months after reference MRC (d) demonstrates severe diffuse stenosis of biliary duct without cystic biliary dilatation. MRC performed 40 months after reference MRC (e) demonstrates cystic biliary dilatation within right lobe of the liver (arrows).



MRC features of PSC

In the first available MRC, performed at a median time of 2.1 months from the diagnosis of PSC, all patients presented abnormalities of both intra- and extrahepatic biliary ducts. All 15 patients had stenosis of intrahepatic biliary ducts. Fourteen of 15 patients had stenosis of the common bile duct. With regard to liver parenchyma, eight of 15 patients had liver dysmorphy. Six patients had features of portal hypertension. Only nine of 15 patients had an arterial phase contrast-enhanced T1-weighted sequence, and among those, eight had a heterogeneous enhancement of the liver parenchyma. Nine of 15 patients had an ANALI score without gadolinium highly predictive of radiological progression (i.e. ≥ 3). Six of nine patients who had gadolinium injection had an ANALI score with gadolinium of 2 (i.e. highly predictive of radiological progression).

In the reference MRC, all 15 patients had severe stenosis of intrahepatic biliary ducts. Fourteen of 15 patients had stenosis of the common bile duct. With regard to liver parenchyma, 12 of 15 patients had liver dysmorphy. Nine patients had features of portal hypertension. Thirteen of 15 patients had an arterial phase contrast-enhanced T1-weighted sequence, and among those, 11 had a heterogeneous enhancement of the liver parenchyma. Moreover, among these 13 patients, 11 had contrast enhancement of the biliary wall. Despite marked variability over time of CD, all PSC worsened on overall primary course. No cases were stable or improved. With regard to MRC features of PSC, we did not observe any significant differences between the three CD groups.

Clinical characteristics

Regarding medical therapy, all patients were treated with ursodeoxycholic acid (UDCA) since PSC diagnosis at a median dose of 15.5 mg/kg/day for 5 months (range, 0–198 months) before

the development of CD. Due to the concomitant presence of overlap syndrome with autoimmune hepatitis (AIH), IBD or other inflammatory disease, 13 (87%) patients underwent immunosuppressive therapy. During the follow-up after the reference MRC, two patients with IBD developed colorectal cancer diagnosed during endoscopic surveillance, seven (44%) patients developed two or more episodes of acute bacterial cholangitis, and two of them underwent multiple therapeutic ERCP. One patient developed a diffuse CCA at the age of 32 years, three patients developed ascites, and two developed hepatic encephalopathy. Because of severe course of the disease, nine (60%) patients have been listed to LT, and eight of them underwent LT in an average of 40 months (range, 6–42 months) after the diagnosis of CD. The median age at the time of LT was 28 years (range, 20–63 years).

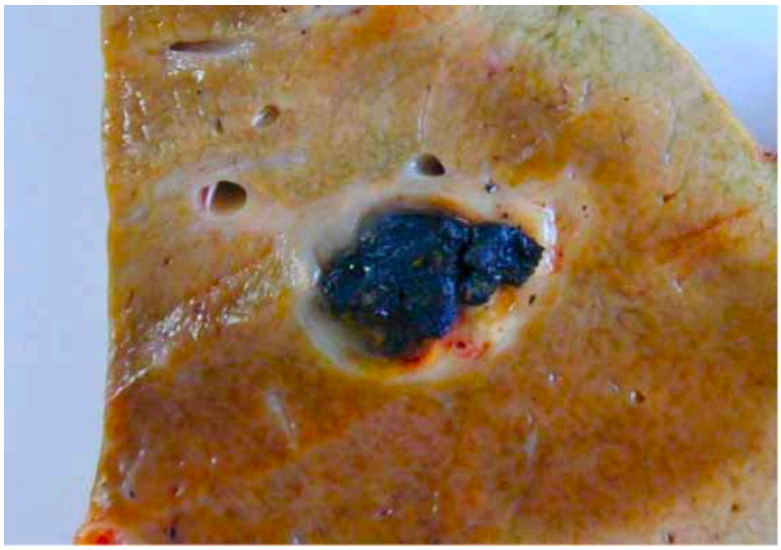
No correlation was observed between the clinical progression observed in all patients and the variable radiological course of the CD.

In the 190 PSC patients without CD, 22 patients underwent LT and 11 patients died during a median follow-up of 9 years (1–35 years). During follow-up patients with CD more frequently developed acute bacterial cholangitis (47% vs. 5%, p = 0.02) and more frequently reached the primary end point (liver transplantation or death) (42% *vs.* 7%, p = 0.003). Histological examination of the eight explanted livers demonstrated the presence of cirrhosis in half of the cases and advanced fibrosis in the other half. All cases showed dilatations of medium and large biliary ducts associated with mural inflammation. Seven cases showed the presence of severe inflammation and presence of ulceration and necrosis of biliary epithelium. The lumen of dilated ducts contained many greenish and brown calculi (Fig. 5) and, in two cases, also polymorphonuclear leukocytes, and an agglomerate of germs and yellowish material.

Five cases showed ductopenia, and two cases showed ductular reaction. Six cases showed periductal concentric fibrosis of medium-size bile ducts, extended to large ducts in five cases

and to small biliary ducts in three cases. Fibro-obliterative lesions were present in five cases. Mild-to-moderate inflammation of the parenchyma (A1 to A2 according to the METAVIR score, used to described activity (necrosis and inflammation) and fibrosis of liver parenchyma[20]) was observed in six cases.

Figure 5. Transversal section of the VII segment of an explanted liver demonstrating a CD of 25 mm of large diameter with whitish bile duct wall and plenty of brown calculi.



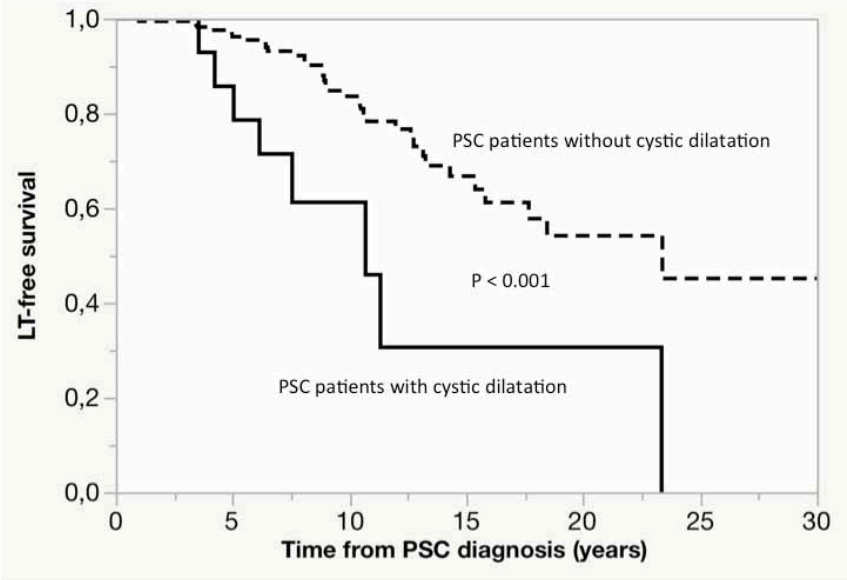
Survival analysis

In the 15 patients with intrahepatic CD of biliary ducts, that half-life without LT was 10.7 years (95% CI 6.6–14.8 years) from the diagnosis of PSC, 4.8 years (95% CI 1.8–7.7 years) from the diagnosis of CD, and 4.2 years (95% CI 0–8.4 years) from the reference MRC.

The 15 patients with CD had a significantly lower survival without LT compared to the control group composed by the other 190 PSC without CD (10.7 vs. 23.4 years, $p < 0.001$).

The 5- and 10-year rates of survival were 79% and 45% in PSC patients with CD versus 96% and 84% in the control group (PSC patients without CD) ($p < 0.001$; HR 3.8 [95% CI 1.7–8.3]) (Fig. 6).

Figure 6. Survival of PSC patients with intrahepatic cystic biliary dilatation (continue line) and control PSC patients without CD (dotted line). Survival of PSC patient with CD is significantly lower than patients without CD ($p < 0.001$).



DISCUSSION

Of the 205 PSC patients with large duct PSC who were followed in our tertiary center, we found that 15 (7.3%) presented with CD. The main characteristic of CD was its marked variability over time with frequent spontaneous improvement or an alternating of improvement and worsening. Because of variability over time of CD we cannot exclude that CD was missed in some patients at their annual MR follow-up, thereby decreasing the true frequency of CD. On the other hand, as the present study was conducted in a tertiary referral center, it is feasible that the occurrence of CD in patients with PSC represents an overestimation with regard to general population with PSC. The patients with CD-PSC were characterized by a young age, a previous history of immunosuppressive therapy in half of them (mostly for the treatment of associated disease), severity of PSC cholangiographic features, and the overall rapid worsening of the disease in all cases with the necessity of LT in half of them. Furthermore, we observed that patients with CD-PSC had an overall survival rate

significantly lower than patients without CD. Indeed, the transplant-free survival from the diagnosis of PSC in patients with CD was 45% at 10 years compared to 84% in PSC patients without CD. Specifically, acute bacterial cholangitis was statistically more frequent in patients with CD, probably because of severe alterations of biliary duct observed in the CD group. Interestingly, we did not find any difference with regard to CD characteristics, PSC features and clinical or radiological evolution between subgroups of patients with a different number of CDs. This suggests that a single CD may have the same prognostic significance as a diffuse pattern and by itself constitutes a cholangiographic marker of more aggressive disease and of poor outcome. Interestingly, biliary wall enhancement at the arterial phase was commonly observed in CD. Such arterial biliary wall enhancement could be the result of biliary wall inflammation, and this marked inflammation could be a key feature in the pathogenesis of CD. This hypothesis is sustained by the observation that 40% of patients had a history of recurrent cholangitis before the development of the maximum size of CD, and the

histological examination of explanted livers showing severe mural inflammation, ulcerations and necrosis of the biliary epithelium. Destructive inflammation was observed in all but one explanted CD-PSC livers, differing from the results previously reported by Harrison and Hubscher, in which it was present in one-third of cases [16]. Ischemia could be an additional mechanism, as severe ischemic cholangitis observed after LT may also exhibit cystic biliary dilatations that may improve during evolution with a pattern similar to our series [21]. On the other hand, we do not assume that cystic dilatation was related to an obstructive pattern because of the specific pattern of cystic dilatation. To our knowledge, this is the first series focusing on this cystic dilated form of PSC. Only six cases with CD of the intrahepatic bile duct were described as sporadic case reports in the literature. As reported in the previously published case reports, we think that it is important to differentiate PSC with CD from other

causes of CD such as Caroli's disease [22] . CD in PSC is easily recognized because of the presence of other biliary signs of PSC such as diffuse intra- and extrahepatic biliary strictures and parenchymal abnormalities, which are not present in Caroli's disease. Moreover, the fluctuant course over time appears to be a characteristic feature of PSC-associated CD, which is never observed in Caroli's disease.

The mechanisms involved in the development of CD in PSC patients are still unknown, but we might suggest a possible role for an acquired defect of tight junctions linked to inflammation that could be responsible for deformation of biliary ducts. Moreover, alterations in cholangiocyte primary cilia, as recently reported in polycystic liver disease, that could lead to an increased cholangiocyte proliferation through TGR5 signaling alterations could be involved[23]. Finally, a role for infection in the CD could be a possibility, since recurrent infections of the biliary tree were observed in these patients of whom half had been treated with immunosuppressive therapy before CD development due to concomitant AIH or IBD. Our group already reported different evolution patterns of usual PSC. In a series of 64 patients, we observed a worsening of radiological features in 37 (58%) patients, whereas the disease remained stable in the other 27 (42%) patients [15]. Observational studies have inherent limitations. The number of patients was relatively low and, because of the retrospective nature of the study, contrast-enhanced sequences were not available for all patients and complete clinical data were missing for some. Therefore, external validation of this single-center experience is required.

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Cystic dilatation of intrahepatic bile ducts: hypothesis regarding the possible pathogenetic mechanisms

The cause for the development of cystic dilatation on intrahepatic bile ducts in patients with PSC is unknown. A pre-stenotic origin of the CD was suggested in three case reports [1–3], on the other hand Theilman *et al.* observed that large intrahepatic cholangiectases were not associated to a downstream stricture since the contrast material rapidly flowed off the cyst when the balloon occluding the cyst was deflated [4]. Moreover, in the explanted liver of PSC patients, Ludwig and colleagues observed that cholangiectases were not the result of passive dilatation of bile ducts [5].

In our study, we described 15 cases of PSC patients with CD of intrahepatic bile ducts not associated to downstream bile duct strictures. Cystic dilatation spontaneously improved in size and number in eight patients and in four patients the course was fluctuant with alternation of worsening and improvement [6]. In one patient the size of the cysts was stable and finally in two patients the size and the number of the CD continue to increase in subsequent radiological follow-up. The spontaneous improvement of the CD therefore suggests that a downstream fibrotic stricture is unlikely the cause for the development of CD. Alternatively, one could envisage that a transient obstruction followed by spontaneous resolution may occur.

We noted that these patients have a severe course of the disease, characterized by rapid clinical and radiological aggravation. Indeed, nine patients were listed for liver transplantation and eight of them were transplanted within 40 months from the diagnosis of the CD. These patients were young (median age 28) at the time of liver transplant and only half of them were transplanted for end-stage liver disease, the other four were transplanted for a significant

impairment of quality of life (pruritus and recurrent acute cholangitis) associated or not with progressive bilirubin increase [6].

We thus had the possibility to review the results of the histological examination performed in the explanted livers. The presence of cirrhosis was documented in half of cases and advanced fibrosis in the other half. All cases showed dilatations of medium and large size biliary ducts associated to mural inflammation. Seven cases showed the presence of severe inflammation and presence of ulceration and necrosis of biliary epithelium. Moreover, a granuloma was identified within the wall of an ulcerated large bile duct in one case and an abscess was observed in another case [6]. We thus briefly discuss previously reported histological findings in PSC patients with intrahepatic bile ducts dilatation in order to assess the presence of similarities.

Ludwig *et al*. reported in five explanted livers of PSC patients the presence of cholangiectases, similar to our CD, and they identified two types of cholangiectases. The first type was characterized by a thick fibrous wall similar to those observed in fibrous cholangitis without ductal dilatation. Differently, the second type had the features of superimposed acute and chronic cellular infective cholangitis. Indeed, the ducts were lined by a thick layer of granulation tissue with granulocytes and other inflammatory cells in the lumen. Moreover, they documented the presence of cholangitis abscesses with entrapped bile pigmented proximal to these areas. Finally, secondary hepatic arteriosclerosis in the vicinity of inflamed cholangiectases was also reported [5].

Harrison and Hubscher, a few years later, documented the presence of inflammatory lesions in intrahepatic dilated bile ducts of 8 explanted livers of PSC patients. Mural inflammation of extrahepatic bile ducts characterized by chronic inflammation, with ulceration of the epithelium and disruption of muscular wall were described. Despite the presence of

neutrophil polymorphs in the lumen, the authors stated that this picture was not that typically associated to acute ascending cholangitis. They rather suggested that this represents a manifestation of disease process [7].

We similarly documented the presence of polymorphonuclear leucocytes, agglomerate of germs and yellowish material inside the CD, moreover, the lumen of dilated ducts was plenty of greenish and black calculi in most of explanted livers.

All these evidences suggest that the inflammatory process is a relevant pathogenetic mechanism in formation of CD and we are now exploring this field by collaborating in a project with **Dr. Tobias Fuchs of Hamburg-Eppendorf University**.

In the last 10 years numerous studies coming from LaRusso group aiming to explain the pathogenesis of polycystic liver disease (PLD) found that cystic cholangiocytes are characterized by malformed cilia [8]. Similar abnormalities in cholangiocyte cilia have been also observed in syndromic and non-syndromic biliary atresia [9].

Cystic cholangiocytes in polycystic liver disease have lost the ciliary-associated TGR5-mediated mechanism that negatively controls cAMP levels and inhibit cell proliferation, thus resulting in cholangiocyte hyperproliferation. They documented that TGR5 is overexpressed and mislocalized in cystic cholangiocytes and its agonists accelerate disease progression by increasing cAMP levels and Gαs expression that results in cell hyperproliferation and cyst growth. Conversely, the pharmacologic inhibition of TGR5 in cystic cholangiocytes *in vitro* or *in vivo* in animal model of PLD attenuates disease progression [10]. The same authors suggest that PSC could be considered as an acquired ciliopathy since they observed that cholangiocyte in this disease possess longer primary cilia compared to normal cholangiocyte and this abnormal elongation determines a consequential impairment on its function [8]. They cited unpublished data showing a decreased expression of TGR5 in human PSC livers. Moreover,

they suggested a possible association between the abnormalities in the production of proinflammatory cytokines and chemokines observed in PSC, and the alterations of TGR5 mediated bile acid signalling. Indeed, previous data demonstrated that TGR5, activated by bile acids, is able to inhibit proinflammatory cytokine production in Kupffer cells thus suggesting a protective role in obstructive cholestasis [11]. Mutations of the gene GPBAR1 codifying TGR5 have been described in PSC livers but their pathogenetic role have not yet been elucidated.

Considering these data together with observations of clinical, radiological and histological evidence of severe inflammation in patients with cystic dilatations, one may speculate that dysfunctional primary cilia and/or an alteration of TGR5 expression and signaling could be implicated in the development of CD. Obviously, what is different from PLD is that in PSC patients the natural evolution of the cysts is variable and, in some cases, cysts also disappeared.

Finally, an interpretation of the CD formation could also be provided by taking into account recent studies on 3D morphogenesis of biliary tree and the adaptive response to cholestasis[12]. Indeed, authors suggested a possible relation between the activation of Ca2+/cAMP signaling [13] by primary cilia on cholangiocytes through sensing bile tonicity and fluid flow and the subsequent actin and tight junction remodeling. They also suggested the possibility to assess whether the mathematical model developed to explain epithelial cyst[14], is adequate to describe the response of biliary tree to the increase of hydrodynamic pressure[12].

In conclusion, different pathogenetic mechanisms possibly implied in the development of intrahepatic bile duct cystic dilatation in PSC have been here proposed and represent fields of future research.

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CHAPTER 9

Endoscopic treatment of benign dominant strictures in Primary Sclerosing Cholangitis: a literature review and a focus on open questions

Nora Cazzagon

INTRODUCTION

PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of biliary tree characterized by the formation of alternating strictures and dilatation of intra- and/or extrahepatic bile ducts [1]. The natural course is often progressive and it could be characterized by the development of dominant strictures (DS) defined as the presence of a stricture, identified by ERCP of CBD with a diameter of ≤ 1.5 mm and/or a stricture of RHD or LHD, within 2 cm of the bifurcation, of ≤ 1.0 mm [2]. The presence of dominant strictures in PSC patients could be associated with the presence of symptoms and elevation of liver enzymes, the presence of CCA or high grade biliary dysplasia. Endoscopic treatment (ET) of DS in PSC has been the topic of different studies published in the last 40 years. The aim of this study was to review the results of endoscopic treatment in patients with benign DS in PSC, focusing on the indication to perform ET, the clinical and cholangiographic features before ERCP, the type and number of treatments, the response criteria used to evaluate the efficacy ET and the post-procedure complications.

MATERIALS AND METHODS

A systematic literature search in PubMed/MEDLINE was conducted, using the search terms "Primary Sclerosing Cholangitis and Endoscopy". Articles were selected by title and their relevance regarding the topic of this review was assessed by review of full-text articles. Articles with content that was considered irrelevant were excluded.

Furthermore, a descriptive analysis regarding the following items was performed:

- Indication to endoscopic treatment.
- Clinical features before endoscopic treatment, with special regards to the description of presence of acute cholangitis, pruritus, jaundice, abdominal pain and fatigue.

- Changes in liver function tests (LFTs) before and after endoscopic treatment.

  These changes were expressed as delta percentage (*Δ%)* and calculated according to the following formula:

  $$\Delta\% = (Value_{Post\text{-}ERCP} - Value_{Pre\text{-}ERCP}) / Value_{Pre\text{-}ERCP} * 100$$

- Cholangiographic findings: localization of dominant strictures, gallstones. Since the formal definition of dominant stenosis was proposed by Stiehl et al. in 2002, we reported, when available, the definition of DS used, for each study.
- Criteria to evaluate response to endoscopic treatment.
- Type and median number of endoscopic treatment.
- Results of endoscopic treatment.
- Post-procedure complications.

RESULTS

Eighteen full-text articles reporting the results of endoscopic treatment of 775 patients with PSC and dominant strictures of bile ducts were included (Table 1). Twelve studies were antecedent to the publication of the formal definition of DS. Most of studies were single-center and retrospective and, in some studies, both patients with and without DS, treated or not with endoscopic treatment were included, thus information was available for the entire population but not for the subgroup of PSC who underwent endoscopic treatment for DS [3]. Finally, nine additional studies which mainly focused on the complications of ET in 1315 PSC patients and the evaluation of risk factors for the development of complications, were also included (Table 2).

Table 1. Studies describing endoscopic treatment of dominant stenosis in patients with PSC.

Author	Period of study	Type of study	Number of PSC patients treated with endoscopic treatment
Johnson *et al.*, 1987 [4]	1983-1987	Retrospective	10
Johnson *et al.*, 1991 [5]	1983-1990	Retrospective	35
Lombard *et al.*, 1991 [6]	1986-1990	Retrospective	6
Lee *et al.*, 1995 [7]	1986-1993	Retrospective	53
Wagner *et al.*, 1996 [8]	1991-1995	Prospective	12
Van Milligen de Wit *et al.*, 1996 [9]	1985-1994	Retrospective	25
Stiehl *et al.*, 1997 [10]	1987-1995	Retrospective	23
Ahrendt *et al.*, 1998 [11]	1980-1994	Retrospective	35
Ponsioen *et al.*, 1999 [12]	1994-1997	Retrospective	32
Baluyut *et al.*, 2001 [13]	1992-1998	Prospective	63
Kaya *et al.*, 2001 [14]	1991-2000	Retrospective	71
Linder and Söderlund *et al.*, 2001 [15]	1987-1997	Retrospective	15
Stiehl *et al*, 2002 [2]	1987-2000	Retrospective	52
Enns *et al*, 2003 [3]	1987-1998	Retrospective	104*
Gluck *et al.*, 2008 [16]	1984-2005	Retrospective	84
Gotthardt *et al.*, 2010 [17]	1987-2006	Retrospective	96
Chapman *et al.*, 2012 [18]	1984-2011	Retrospective	80
Ponsioen *et al.*, 2018 [19]	2011-2016	Prospective	65
Total number of PSC patients			**775**

*This number included both patients having only diagnostic and therapeutic ERCP.

Table 2. Studies focusing on complication of ERCP in PSC.

Author	Period of study	Type of study	Number of PSC patient	Number of procedure
Beuers *et al.*, 1992 [20]	1985-1990	Retrospective	15	15
Van Milligen de Wit *et al.*, 1997 [21]	1994-1995	Prospective	16	42
Van den Hazel *et al.*, 2000[22]	NA	Prospective multicentric	83	106
Etzel *et al.*, 2008 [23]	1998-2000	Retrospective cross-sectional	30 PSC 45 non-PSC	85 in PSC 70 in controls
Bangarulingam *et al.*, 2009 [24]	2005	Retrospective	168 PSC 981 non-PSC	308 in PSC 1268 in non-PSC
Alkhatib *et al.*, 2011 [25]	2000-2009	Retrospective	75	185
Ismail *et al.*, 2012 [26]	2007-2009	Retrospective	443	NA
Navaneethan *et al.*, 2015 [27]	1998-2012	Retrospective	294	657
Von Seth *et al.*, 2015 [28]	2007-2009	Retrospective	141 PSC 8791 non-PSC	NA
Total number of PSC patients			**1315**	

Definition of dominant strictures

Among the 18 studies, only seven reported the definition used to identify DS, which was based in all cases on cholangiographic features found at ERC [2,6,8–10,12,17]. Lombard *et al.* defined the DS as the presence of a reduction of at least 50% of the calibre of the bile duct at hilum or in EHBD [6]. Four subsequent studies defined the presence of DS according the spatial localization but they did not quantify the reduction of the calibre of the bile duct [8–10,12]. Stiehl *et al.* in 2002 proposed the well-known definition of DS based on a measure of the severity of the EHBD strictures [2]. Some of the main issues regarding this definition are the fact that the quantification of the stricture depends on the filling pressure of the medium contrast injection and that it doesn't take into account the clinical relevance of the stricture.

Indications to endoscopic treatment

Overall the main indication to perform ERCP with endoscopic treatment was the presence of acute cholangitis or jaundice (Table 3). Early in the nineties, the Dutch group reported that they considered the progression of cholestatic enzymes correlated to the presence of EHBD strictures an indication to ERCP as well as the presence of one or more symptoms related to cholangitis [9]. A similar view was also reported in three subsequent German studies from Stiehl's group [2,10,17]. Ponsioen *et al.* in 1999, define the presence of at least one DS with associated symptoms as an indication to endoscopic intervention. Moreover, they proposed a scale for the quantification of cholestatic symptoms (Amsterdam Cholestatic Complaints Score) [12]. This scale was a relevant novelty since it allowed, for the first time, to quantify the impact of endoscopic intervention on the treatment of symptoms in PSC patients with DS. Then, in 2008, Gluck *et al.* proposed, besides the classical indication, a new indication represented by the radiological worsening, documented with radiographic studies other than

ERCP, associated to a new appearance of a right side abdominal pain. This was the first study that applied the idea that imaging studies other than ERCP, *i.e.* MRCP, could have been helpful to assess the indication to ET in PSC patients. The concept of radiological worsening, evaluated by MRCP, as indication to ERCP has been incorporated, 10 years after, in the current European guidelines [29]. Finally, in the recent multicentric international DILSTENT trial, the presence of a dominant-appearing strictures at MRCP was included in the inclusion criteria together with different grades of clinical and biochemical worsening [19]. On the other hand, the definition of a dominant-appearing strictures at MR cholangiography was not provided.

Table 3. Indication to endoscopic treatment of dominant strictures in PSC patients

Author	**Indications**
Johnson *et al.*, 1987 [4]	Prior acute cholangitis
Johnson *et al.*, 1991 [5]	Major ductal strictures + symptoms related to cholangitis or jaundice
Lombard *et al.*, 1991 [6]	Severe strictures + deep jaundice (onset within 6 months)
Lee *et al.*, 1995 [7]	Cholangitis, jaundice or abdominal pain if strictures of EHBD and RHD or LHD, stones
Wagner *et al.*, 1996 [8]	Major ductal strictures and symptoms related to cholangitis or jaundice
Van Milligen de Wit *et al.*, 1996 [9]	One or more signs or symptoms related to cholangitis, jaundice (onset within 3 months), right upper quadrant pain or progression of cholestatic enzymes related to EHBD strictures
Stiehl *et al.*, 1997 [10]	Development of major duct stricture during ERCP follow-up and biochemical evidence of cholestasis
Ahrendt *et al.*, 1998 [11]	DS extrahepatic and hilar
Ponsioen *et al.*, 1999 [12]	DS with associated symptoms
Baluyut *et al.*, 2001 [13]	DS
Kaya *et al.*, 2001 [14]	One or more symptomatic DS
Linder and Söderlund *et al.*, 2001 [15]	DS associate to cholestatic biochemical profile or symptoms
Stiehl *et al*, 2002 [2]	DS and biochemical evidence of cholestasis
Enns *et al*, 2003 [3]	Indication to ERC: Jaundice, fever, pruritus, abdominal pain and asymptomatic elevation in liver enzymes or FU
Gluck *et al.*, 2008 [16]	Indication to ERC: recurrent AC unresponsive to antibiotic therapy, worsening of jaundice +/- increase of pruritus or new right side abdominal pain + worsening LFTs and/or radiographic studies
Gotthardt *et al.*, 2010 [17]	DS and biochemical evidence of cholestasis
Chapman *et al.*, 2012 [18]	DS amenable to therapeutic intervention
Ponsioen *et al.*, 2018 [19]	Different criteria including cholestatic worsening, worsening of symptoms and/or a documented dominant-appearing stricture on MRCP or ERCP.

Clinical and cholangiographic presentation at the time of ERCP

At the time of ERCP up to 100% of PSC patients had one or more symptoms of the disease including pruritus, fatigue, abdominal pain, jaundice and acute cholangitis (Table 4). The presence of acute cholangitis was documented in eight studies, its frequency ranges between 17-83% and it represented an exclusion criteria in the DILSTENT trial [19]. Jaundice at the time of ERCP was present in 17-67% of patients [2,5,9,11,13–15,17], frequently associated to pruritus or acute cholangitis. Abdominal pain alone, or as symptom of acute cholangitis, was reported in most of studies and it was present in up to 73% of patients in one study [15].

Cholangiographic findings at the time of endoscopic intervention were reported in thirteen studies (Table 3). Overall, the presence of a DS in CBD or CHD ranges between 56-100% of patients, in RHD or LHD between 11-38% and both in CBD and RHD or LHD in 19-72%. Three studies described the type of PSC localization that was intra- and extrahepatic in 100% of patients [6,8,15]. Finally the presence of biliary stones was documented in up to 51% of patients[16].

Table 4. Clinical features and cholangiographic findings at the time of ERC

Author	Clinical features	Cholangiographic findings
Johnson *et al.*, 1987 [4]	NA	NA
Johnson *et al.*, 1991 [5]	29 (83%) AC 6 (17%) JAUN	- Mean 3.3 strictures/patients - Radiologic score for strictures
Lombard *et al.*, 1991 [6]	6(100%) PRU or FAT 2 (33%) rec AC	- All intra- and extrahepatic PSC - 5(83%) long DS of CBD - 2(33%) DS in CBD, CHD and RHD/LHD
Lee *et al.*, 1995 [7]	20 (38%) AC	- 18(34%) DS - 10(19%) stones
Wagner *et al.*, 1996 [8]	100% symptomatic (FAT, PAIN, PRU). Symptom score (0-9)	- 100% intra- and extra- - 2.1 DS per patients - Johnson' score for strictures mean 3.2
Van Milligen de Wit *et al.*, 1996 [9]	24% AC 36% JAU 14% AC + JAU 28% biochemical worsening + PRU or RUQP	Localization of DS within the 27 stent periods: - 15 (56%) in CBD - 4 (15%) in CHD - 3 (11%) in RHD or LHD - 5 (19%) in two sites
Stiehl *et al.*, 1997 [10]	NA	- 100% with DS - 2 patients with stones
Ahrendt *et al.*, 1998 [11]	94% symptomatic: - 67% JAU - 38% PAIN - 48% PRU - 17% AC	NA
Ponsioen *et al.*, 1999 [12]	- 50% PRU - 70% FAT - 50% RUQP - 18% AC	NA
Baluyut *et al.*, 2001 [13]	56(89%) symptomatic: - 67% JAU - 49% AC	NA
Kaya *et al.*, 2001 [14]	- 13(18%) recurrent AC and PAIN - 58(82%) symptoms and hyperbilirubinemia	- 26(37%) pts with one or more DS in EHBD - 7 (10%) pts with DS in IHBD - 38 (53%) pts with IHBD and EHBD - 33 (46%) pts with stones
Linder and Söderlund *et al.*, 2001 [15]	- 11(73%) PAIN +/- JAU - 4 (26%) cholestatic profile	- All Intra- and extrahepatic PSC - 3 (20%) with DS at hilum - 6 (40%) with DS at the level of or distal cystic duct - 6 (40%) in both
Stiehl *et al*, 2002 [2]	30 (58%) symptomatic: - 17(32%)JAU - 7(13%) JAU and PRU - 6(14%) PRU	- 52 (100%) CBD - 7 (14%) RHD - 4 (8%) LHD - 21 (40%) RHD + LHD
Enns *et al*, 2003 [3]	NA	NA
Gluck *et al.*, 2008 [16]	NA	51% with biliary stones
Gotthardt *et al.*, 2010 [17]	- 32(33%) JAU - 11(11%) PRU	- 100% with DS in CBC - 72% with DS also in RHD and/or LHD
Chapman *et al.*, 2012 [18]	NA	- 47(59%) in CBD - 11(14%) in CHD - 22(27%) at the hilum
Ponsioen *et al.*, 2018 [19]	0 AC ACCS total 4 (2-5)	- 52-68% in CBD - 48-50% in CHD - 38-45% hilar - 34-38% in LHD - 36-38% in RHD

Abbreviations: AC, acute cholangitis; NA: indicates not available information; JAU, jaundice, PRU, pruritus; FAT, fatigue; PAIN, abdominal pain; RUQP, right upper quadrat abdominal pain; ACCS: Amsterdam Cholestatic Complaint Scale; DS, dominant strictures; CBD, common bile duct; CHD, common hepatic duct; RHD, right hepatic duct; LHD, left hepatic duct; EHBD, extrahepatic bile duct.

Type and number of endoscopic treatment

In all but two studies an antibiotic prophylaxis prior to ERCP was reported and it was mostly represented by *i.v.* administration of beta lactams and/or cephalosporins [2,4–10,12–19]. The type of endoscopic treatment varies between different group and according different years (Table 5). The German group preferred to treat DS with repeated, each 4 weeks, endoscopic balloon dilatation and, in selected patients with severe cholestasis and bacterial cholangitis, they considered a stent placement for 1-2 weeks and then eventually replaced for other 2 weeks for a total duration of 2-4 weeks [2,10,17]. Other groups used to place a stent, based on endoscopist evaluation, if the stricture diameter was not significantly increased after dilatation [5,7,9,11,13–16,18]. In these studies the duration of stent was longer compared with the stent duration described by the German group and ranges between 1 and 4 months [5,7,9,13,14]. A strategy, adopted from the Dutch group to avoid stent clotting, was the short-term stent placement (mean stent duration of 11 days) which demonstrated to be effective and safe with a beneficial effect sustained for several years [12]. The recent DILSTENT trial, a multicentric, randomized trial comparing balloon dilatation with short term stenting for the treatment of DS, confirmed that stents were not superior to balloon dilatation for the treatment of DS in patients with PSC but a significant higher rate of serious adverse events occurred in the short-term stent arm [19]. The number of endoscopic procedures to treat a DS varies between studies and according to the type of treatment with a reported mean of 2.1-5.2 endoscopic dilatations needed to treat a DS and the majority of the procedures were performed during the first year [2,10,13,14,17].

Table 5. Type and number of endoscopic treatment for dominant strictures in PSC patients.

Author	Type of ET	Number of procedure
Johnson *et al.*, 1987 [4]	EBD/stent	-
Johnson *et al.*, 1991 [5]	EBD in 24(69%) EBD in 11(31%)	-
Lombard *et al.*, 1991 [6]	EBD/stent in 5(83%) EBD in 1	12 procedures in 6 patients
Lee *et al.*, 1995 [7]	EBD in 31(58%) Stent in 22(42%) NBD in 8(15%) Stones extraction in 12(23)	100 procedures in 53 patients
Wagner *et al.*, 1996 [8]	EBD + NBD	3(2-9) EBD per patient
Van Milligen de Wit *et al.*, 1996 [9]	Stent +/- EBD Stones extraction	105 in 25 patients
Stiehl *et al.*, 1997 [10]	EBD +/- Stent	91 (mean 4.5 per patient, 2.87 in the first year and rapid decrease)
Ahrendt *et al.*, 1998 [11]	EBD +/- Stent	119 (mean 3.2 per patient)
Ponsioen *et al.*, 1999 [12]	Short term stent	45 procedures in 32 patients
Baluyut *et al.*, 2001 [13]	EBD +/- Stent 97% EBD 52% stent	Mean 3.3 EBD Mean 2.2 stent
Kaya *et al.*, 2001 [14]	EBD +/- Stent 34 (48%) EBD 37 (52%) Stent endoscopic and/or percutaneous	73 procedures in 34 pts (mean 2.1) 243 procedures (80 endoscopic, mean 2.5; 163 percutaneous, mean 7)
Linder and Söderlund *et al.*, 2001 [15]	EBD +/- stent	43 procedures in 15 patients
Stiehl *et al*, 2002 [2]	EBD +/- stent	210 EBD (mean 4.5) in 52 patients
Enns *et al*, 2003 [3]	EBD +/- stent	148 therapeutic procedures: 40% EBD 20% stent insertion 12% stent extraction 9% stone extraction
Gluck *et al.*, 2008 [16]	EBD +/- stent	291 procedures in 84 patients: 160 EBD 84 stent 73 stone removal
Gotthardt *et al.*, 2010 [17]	EBD +/- stent	500 EBD (mean 1.8) in 96 patients 5 stent
Chapman *et al.*, 2012 [18]	Stent +/- EBD	46% stent 20% EBD 17% EBD+stent 17% no or failed intervention
Ponsioen *et al.*, 2018 [19]	EBD *vs.* Short-term stent	

Abbreviations: EBD, endoscopic balloon dilatation, NA, information not available.

Response criteria and results of ERCP

The criteria of response to endoscopic treatment included the evaluation of clinical, biochemical and radiological improvement, the technical success and the observed survival. Clinical improvement was differently defined among different studies as the reduction of the number of hospitalizations for acute cholangitis [4,5] or the reduction of symptoms. This last, was defined in different ways as: the complete resolution of symptoms [3,6], the significant change in symptoms quantified or not according symptoms' scores [8,12,14–16,19], the significant changes in percentage of patients with symptoms [9] or the subjective improvement reported by the patients [7]. The radiologic improvement was adopted by Johnson *et al.* in 1991 as a measure of ET effectiveness and it was also applied in subsequent studies [5–8]. On the other hand, biochemical improvement was defined in most studies as a significant reduction of cholestatic enzymes compared with the baseline values and in one study an actual criterion of biochemical response was proposed. Indeed, Enns *et al.* defined as laboratory successful outcome the improvement in 2 liver enzymes (AST, ALT, ALP) by greater than 50%, or resolution of jaundice. In this study the authors defined two criteria of success, able to distinguish responders and non-responders to ERCP, in order to analyse the predictive factors of response to the procedure. The limit of this study is that they included both diagnostic and therapeutic ERCP and both patients with and without DS and the results were representative of the entire population [3]. In other studies, the impact of ET on survival of PSC patients was used as a measure of effectiveness by comparing the observed and the predicted survival estimated by the original PSC Mayo model [2,10,17] or the Revised PSC Mayo model [13,16] . Finally, as reported above, in DILSTENT trial, the primary end-point used to compare effectiveness of endoscopic balloon dilatation and short-term stenting was the cumulative recurrence-free rate of the primary DS within the study follow-up [19].

The results of ET according to the different criteria are detailed in Table 6 and overall ET of DS in symptomatic PSC has been demonstrated to reduce to number of hospitalization for acute cholangitis, to reduce and even to resolve symptoms of the disease, to significantly improve biochemical features, to improve the cholangiographic features, and to ameliorate survival compared with the predicted survival estimated by the Mayo model. Analysing the twelve studies that reported baseline and post treatment biochemical values, a range of reduction of 60-97% of total bilirubin, 6-60% of alkaline phosphatase, 20-59% of transaminases and 24-45% of GGT was found. A mean reduction of 70%, 30%, 40% and 36% of total bilirubin, ALP, transaminases and GGT, respectively, was obtained pooling together the results of different studies [2,4–6,9,12,15,17,19]. With the limits explained above (inclusion of both therapeutic and diagnostic ERCP and both presence or not of DS), Enns *et al.* reported that the predictive factors of success of ERCP were the presence of DS, the ET, a high serum bilirubin at baseline and the presence of CBD stricture.

Table 6. Response criteria and results of endoscopic treatment for DS in PSC patients.

Author	Response criteria	Results of ERCP
Johnson *et al.*, 1987 [4]	- Clinical improvement (reduction in number of hospitalization) - LFTs improvement	- N. of hospitalization ↓ - LFTs ↓
Johnson *et al.*, 1991 [5]	- Clinical improvement (reduction in number of hospitalization for AC) - LFTs improvement - Radiologic improvement (Johnson' score)	- N. of hospitalization ↓ - Total bilirubin ↓ - Radiologic score ↓
Lombard *et al.*, 1991 [6]	- Clinical improvement - LFTs improvement - Radiologic improvement (ERCP)	- 5(83%) Resolution of pruritus - Total bilirubin, ALP ↓ - 4(67%) radiologic improvement
Lee *et al.*, 1995 [7]	- Technical success - Clinical improvement - LFTs improvement - Radiologic improvement	- 88% of technical success - 41(77%) clinical improvement defined as - 28(53%) subjective improvement - 39% LFTs improvement - 50% radiologic improvement
Wagner *et al.*, 1996 [8]	- Clinical improvement - LFTs improvement - Radiologic improvement according Johnson' score	- Symptoms score ↓ - LFTs ↓ - Radiologic score ↓
Van Milligen de Wit *et al.*, 1996 [9]	- Technical success - Clinical improvement - LFTs improvement	- 84% technical success - Decrease of: jaundice (62% > 14%), RUQP (52%>14%), pruritus (52%>5%), fever (38% to 10%) - Stable LFTs ↓
Stiehl *et al.*, 1997 [10]	- Observed vs. predicted survival by Mayo Model[30]	- Observed survival better than predicted survival
Ahrendt *et al.*, 1998 [11]	- Survival comparison between different treatment - Total bilirubin improvement	- Lower survival than surgical resection - No significant reduction of total bilirubin after treatment
Ponsioen *et al.*, 1999 [12]	- Technical success - LFTs improvement at 2 months - Clinical improvement (Semiquantitative Scoring of cholestatic complaints)	- 100% improvement of DS - 83% improvement on cholestatic complaints - LFTs ↓
Baluyut *et al.*, 2001 [13]	- Observed vs. predicted survival estimated by Revised Mayo model[31]	- Observed survival rate higher than the predicted survival
Kaya *et al.*, 2001 [14]	- Clinical response (changes in LFTs and symptoms)	- In EBD group: jaundice and fever↓ total bilirubin and ALP ↓ - In stent group: jaundice ↓ total bilirubin ↓
Linder and Söderlund *et al.*, 2001 [15]	- LFTs improvement - Clinical response - Radiologic improvement	- 47% with LFTs ↓ - 53% with clinical improvement - 80% with radiologic improvement
Stiehl *et al*, 2002 [2]	- Technical success - Observed survival compared predicted survival by Mayo model - Clinical improvement	- 100% in CBD 88% of DS above the bifurcation - Observed survival higher than predicted survival - 100% with jaundice ↓ 92% with pruritus ↓
Enns *et al*, 2003 [3]	- Clinical success: resolution of the primary presenting symptoms - Laboratory success: improvement in 2 liver enzymes (AST, ALT, ALP) by greater than 50%, or resolution of jaundice	- 70% with clinical improvement <u>Predictors of clinical success</u> (overall): DS, ET, high serum bilirubin. - 52% with laboratory improvement <u>Predictors of successful laboratory outcome</u> (overall): DS, CBD stricture, ET.
Gluck *et al.*, 2008 [16]	- Comparison between observed and predicted survival estimated by Mayo model [31]	- Observed survival higher than the 3- and 4-years survival predicted by Mayo model.
Gotthardt *et al.*, 2010 [17]	- Clinical improvement - LFTs improvement	- 100% with pruritus improvement - LFTs ↓
Chapman *et al.*, 2012 [18]	NA	NA
Ponsioen *et al.*, 2018 [19]	- Recurrence-free rate of the primary DE within 24 months - Clinical improvement - LFTs improvement	- No significant difference in recurrence-free rate between the two groups - 77% clinical improvement - LFTs ↓

Abbreviation: NA, information not available, LFTs, liver function tests, ↓ indicates the presence of a significant reduction of LFTs or symptoms and/or radiologic score after the endoscopic treatment.

Post-procedures complications in PSC patients

We identified overall twenty-seven studies that reported the frequency of post-procedure complications in patients with PSC (Table 7 and 8). Post-procedure complications in PSC were more frequently pancreatitis, ascending cholangitis, post-sphincterotomy haemorrhage and bile duct perforation. Other complication included: gallbladder hydrops, cholecystitis, liver abscess, stent occlusion, acute stent migration, bacterial peritonitis, sepsis and ascites.

The frequency of complications was variably reported as percentage of patients with complications and/or as percentage of procedures with complications since many patients underwent multiple procedures to treat a primary DS. Not all the studies reported the two percentages. Moreover, the first published studies included a limited number of patients and thus the percentage of patients with complications resulted considerably high [5–8]. Furthermore, focusing on the eight studies that specifically addressed this issue, the reported frequency of post-procedure complications is 4 - 18% [21–28]. An increased frequency of post - ERCP pancreatitis (PEP), cholangitis and per-operative extravasation of contrast in PSC patients compared to non-PSC patients was reported [28] and PSC appeared to be an independent risk factor for PEP. Risk factors for post-procedure complications in PSC patients were young age, female sex, pancreatic duct cannulation, dilatation of a BD stricture and the complexity of the technique [25–28].

Table 7. Post-procedure complications within the 18 studies reporting endoscopic treatment of DS in PSC**.**

Author	Type of complications	Patients with complications	Procedures with complications	% of patients with SAE	% of procedures with SAE
Johnson *et al.*, 1987 [4]	Mild PEP	1(10%)	NA	0	NA
Johnson *et al.*, 1991 [5]	Overall: - AC - GI bleeding post sphincterotomy - PEP requiring hospitalization	8(23%) 6 (17%), 5 post-stents 1(3%) 1(3%)	NA	2(6%)	NA
Lombard *et al.*, 1991 [6]	Overall: - Post ERCP bacteraemia - Gallbladder percutaneous drainage - Cholecystectomy	4(66%) 2(33%) 1(17%) 1(17%)	4(33%)	2(33%)	2(17%)
Lee *et al.*, 1995 [7]	Overall: - PEP - AC	15(28%) 7(13%) 8 (15%)	15(15%)	3(6%)	3(3%)
Wagner *et al.*, 1996 [8]	Overall: - Mild pancreatitis - GI bleeding post sphincterotomy - AC	5(42%) 1(8%) 1(8%) 3(24%)	NA	0	NA
Van Milligen de Wit *et al.*, 1996 [9]	Overall: - AC - PEP - GI bleeding post sphincterotomy	-	15(14%) 10(10%) 4(4%) 1(1%)	2(8%) 1 severe PEP 1 severe AC with septic shock	2(2%)
Stiehl *et al.*, 1997 [10]	Overall: - PEP - AC - CBD perforation	8(35%) 5(22%) 2(9%) 1(4%)	11(12%) 7(8%) 3(3%) 1(1%)	1(4%)	1(1%)
Ahrendt *et al.*, 1998 [11]	Overall: - PEP - AC	5(14%) 4(11%) 1(3%)	5(4%)	0	0
Ponsioen *et al.*, 1999 [12]	Overall: - BD Perforation - PEP - Gallbladder hydrops	- 3(9%) 2(6%)	7(15%) 2(4%) 3(7%) 2(4%)	0	0
Baluyut *et al.*, 2001 [13]	Overall: - BD Guidewire perforation - BD perforation due to dilatation - PEP - Delayed AC	13(21%) 5(8%) 5(8%) 2(3%) 1(2%)	NA	1(2%)	NA
Kaya *et al.*, 2001 [14]	Overall: - CBD or CHD perforation - AC and sepsis - PEP - Haemorrhage post sphincterotomy - Haemobilia - Bacterial peritonitis, liver failure and death	25(35%), higher in PTC +/- stent group 7(10%) 5(7%) 1(1%) 1(1%)	36(11%), higher in PTC +/- stent group	1(1%)	NA
Linder and Söderlund *et al.*, 2001 [15]	Overall: - AC - 2 persistent jaundice	7(47%) 5(33%) 2(13%)	NA	NA	NA
Stiehl *et al*, 2002 [2]	Overall: - PEP - CBD perforation	10 (19%) 9 (17%) 1 (2%)	12(6%) 11(5%) 1(0.5%)	1(2%)	1(0.5%)
Enns *et al*, 2003 [3]	Overall:	NA	27(18%)	NA	7(5%) 1 BD injury 1 hepatic abscess 4 PEP 1 AC
Gluck *et al.*, 2008 [16]	Overall: - PEP - AC - Sepsis - BD perforation - Post sphincterotomy bleeds - Liver abscess	21 (25%) 10 (12%) 3 (4%) 3 (4%) 2 (2%) 2 (2%) 1 (1%)	21(7.2%) 10 (3%) 3 (1%) 3 (1%) 2 (0.7%) 2 (0.7%) 1 (0.3%)	NA	NA
Gotthardt *et al.*, 2010 [17]	Overall: - PEP - AC - CBD perforation	16(17%) 9 7 1	16(3%) 11 4 1	1(1%)	1(0.1%)
Chapman *et al.*, 2012 [18]	Overall: - Minor BD perforation - PEP - AC	5(6%) 2 2 1	5 (1%)	2 (3%) 1 (1%) 1 (1%)	NA
Ponsioen *et al.*, 2018 [19]	Overall: - AC - PEP - Post-ERCP pain - Ascites	NA	NA	17 (27%) 5 (8%) 9(14%) 2(3%) 1(1.5%)	Higher risk of SAEs in short term stent group mainly for PEP with intact papilla

Table 8. Studies focusing on post-procedure complication in PSC patients**.**

Author	Type of ERCP	Complications
Beuers *et al.*, 1992 [20]	Diagnostic	Deterioration of cholestasis after ERC is associated with advanced disease, and advanced histological changes and a priori abnormal serum bilirubin levels appeared to be important predictors.
Van Milligen de Wit *et al.*, 1997 [21]	Therapeutic (short-term stenting)	7% procedure-related complications. Number of patients with complication: - 2 small perforation of the stricture site - 1 moderately severe PEP 19% of patients with complications
Van den Hazel *et al.*, 2000[22]	Diagnostic (53%), Therapeutic (47%)	9.4% procedure-related complications. Number of patients with complications: - 2 cholangitis - 3 PEP - 1 post-sphincterotomy bleeding - 1 perforation - 1 worsening of symptoms - 1 venous thrombosis in arm. 11% of patients with complication Higher frequency of complication in therapeutic group. RR 7.2 vs. 4.5
Etzel *et al.*, 2008 [23]	Diagnostic (22%), Therapeutic (75%)	12.9% procedure-related complications: - 2 PEP - 5 cholangitis - 1 bleeding - 1 hypoxia - 1 liver abscess 27% of patients with complications. No increased risk of complications in PSC compared with patients with biliary strictures who do not have PSC.
Bangarulingam *et al.*, 2009 [24]	Therapeutic	11% procedure-related complications in PSC vs. 8% in non-PSC (P=N.S.) Incidence of cholangitis higher in PSC compared with the control group (4% vs. 0.2%, p<0.0002) and correlated with the length of the procedure. Number of complication were increased over diagnostic studies when more than 5 interventions were performed. Number of PSC patients with complications: - PEP 9 (5%) - Cholangitis 6 (4%) - Perforation 3 (2%)
Alkhatib *et al.*, 2011 [25]	Diagnostic and therapeutic	14% procedure-related complications: - PEP 9(5%) - Cholangitis 2(1%) - Cholecystitis 1(0.5%) - Stent occlusion 1(0.5%) - Acute stent migration 1(0.5%) - Bile leak 1(0.5%) Risk factor for post-ERCP complication: Specific endoscopist; Biliary dilatation; Sphincterotomy; Presence of cirrhosis; Crohn disease; AIH
Ismail *et al.*, 2012 [26]	Diagnostic and therapeutic	9% post-procedure complications: - PEP 7% (severe in 0.7%). - Cholangitis 1.4% (not correlated to a longer ERCP) - BD perforation 0.6% Risk factors for PEP: Female sex; Young age; Complexity of technique (precut + biliary and pancreatic sphincterotomy); N. of times wire in pancreas; Sphincterotomy; Radiologic score
Navaneethan *et al.*, 2015 [27]		4.3% post-procedure complications: - PEP 1.2% - cholangitis 2.4% - bleeding
Von Seth *et al.*, 2015 [28]		18.4% post-procedure complications (increased compared to non-PSC, 7.3%): - PEP 7.8% vs. 3.2% in non-PSC p=0.002 - cholangitis 7.1% vs. 2.1% in non-PSC, p<0.001 - per-operative extravasation of contrast 5.7% vs. 0.7% in non-PSC, p< 0.001 PSC is a independent risk factors for PEP! Risk factors for AE overall: - PSC - Cannulation of the pancreatic duct - Dilatation of a biliary stenosis.

DISCUSSION

This literature's review focusing on description of endoscopic treatment of patients with PSC and dominant strictures allows to derive some conclusions and some open questions.

First, most of studies included patients with PSC who developed during follow-up evident symptoms of the disease (acute cholangitis, jaundice, pain, pruritus) and due to these symptoms, they underwent ERCP as first diagnostic modality to look for, and eventually to treat, a dominant stricture. When found, the DS associated with a clinical worsening constituted the indication to the endoscopic treatment in most of the studies. Moreover, in some centers a regular endoscopic follow-up with ERCP was in place and the discovery of a DS during follow up represented *per se* the indication to ET. The definition of DS varies among different studies also after the introduction of the quantitative definition by Stiehl *et al.* but, in general, we observed that in clinical practice most of treated patients were symptomatic thus indicating that not only the dimensional reduction of the calibre of the ducts but also the clinical relevance need to be added to the definition of dominant stricture. A lower percentage of patients who underwent endoscopic follow-up have been treated for the presence of DS *per se*, and not for clinical worsening. In these studies, the overall criteria of response was based on the comparison between observed and predicted survival estimated by the Mayo model that was in favour of the actual survival observed in treated patients. Thus, one may infer that patients with DS but without clinical symptoms, as well as patients with symptoms, may benefit of endoscopic treatment of strictures at least in term of observed *vs.* predicted survival. But this is in contrast with current European guidelines that suggests to perform treatment with brush sampling of suspected significant strictures identified at MRC in patients who present symptoms likely to improve after the endoscopic treatment. This is a strong

recommendation but with a low quality of evidence since, up to now, no studies were aimed to identify predictive factors of improvement after endoscopic treatment. One of the reason for that, could be the lack of an objective criteria of response to endoscopic treatment correlated to an evident improvement in survival of these patients. Indeed, despite the resolution of acute symptoms and the exclusion of the presence of malignancy within the stricture, it is not clear whether the treatment of an EHBD stenosis could delay progression of the disease and improve survival. Indeed, previous ERCP-based studies demonstrated that intrahepatic cholangiographic changes have more relevant prognostic significance than extrahepatic cholangiographic changes [32,33]. Similarly, a recent French study based of MRI found that the severity of intrahepatic biliary dilatations but not the extrahepatic bile ducts strictures was independently correlated with radiologic progression of patients with PSC [34]. Thus, one of the open questions is whether patients with DS who underwent endoscopic treatment have an actual advantage in term of long-term survival and a delayed disease progression compared to patients with dominant stenosis who did not underwent to endoscopic treatment. It's clear that this point could not be addressed, for ethical reason, evaluating patients with DS and a clear clinical indication (acute cholangitis, jaundice, pruritus and/or suspicion of CCA) but rather patients with DS found at imaging and without a clear clinical indication. Indeed, it is not clear if the latter group may benefit of endoscopic treatment as well as patients with a clear indication. MRCP nowadays has replaced ERCP in the diagnosis of PSC and it the first imaging modality recommended in case of aggravation of symptoms. Moreover, it is used in different centers in follow-up of PSC patients.

In conclusion, since an always larger number of severe stenosis will be identified by MRI, it becomes fundamental to identify magnetic resonance cholangiographic criteria to define

dominant stenosis and predictive criteria of response to endoscopic treatment in order to optimize the selection of candidates to the procedure.

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CHAPTER 10

Magnetic resonance cholangiography and biochemical predictive criteria of response to endoscopic treatment of severe strictures in patients with primary sclerosing cholangitis

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ABSTRACT

Background

The aim of this study was to identify predictive criteria of improvement after endoscopic treatment (ET) for severe strictures of extrahepatic bile ducts in patients with primary sclerosing cholangitis (PSC).

Methods

Patients with PSC with at least one ET for severe stricture were included. Magnetic resonance cholangiography (MRC) features were evaluated according to a standard model of interpretation and a radiologic qualitative score of probability of improvement after ET was built. Score 3 (likely) was given in severe common bile duct (CBD) stricture with marked dilatation without severe strictures of upstream ducts, score 1 (unlikely) was given in case of severe multiple strictures of secondary ducts without biliary dilatation and score 2 (undeterminate) was given to an intermediate pattern. Response to ET, assessed at 2 and 12 months from inclusion, was defined by the presence of at least one clinical criterion (resolution of jaundice or acute bacterial cholangitis, resolution or amelioration of right upper abdominal pain or pruritus) or the biochemical criterion (concomitant reduction of at least 40% from baseline values of total bilirubin, alkaline phosphatase and GGT).

Results

31 patients were included. All had severe stricture (reduction≥75% of the diameter) of CBD and 50% had a severe stricture of right and/or left hepatic duct (LHD) at MRC. According to the qualitative score, 16 patients had score 3, 7 had score 1 and 9 had score 2. T12-response was obtained in 50% of patients. By univariate analysis, short LHD strictures, bilirubin, transaminases, pruritus and score 3 were associated to T12-response. Higher bilirubin and

transaminases were independent predictive factors of T12-response (HR 24,95%CI:3.4-170.4, p=0.001 and 23.8,95%CI3.4-169.4, p=0.002, respectively).

Conclusion MRC, together with biochemical features, may contribute to identify PSC patients likely to improve after ET for severe strictures of EHBD.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive fibrotic obliteration of intra- and/or extrahepatic bile ducts [1]. The natural course of the disease could be characterized by worsening of symptoms such as pruritus and abdominal pain or the occurrence of acute cholangitis and jaundice that are due in a portion of these patients to the development of dominant strictures (DS). The term "dominant" defines the presence, at endoscopic retrograde cholangiopancreatography (ERCP), of a stricture of common bile duct (CBD) with a diameter of ≤ 1.5 mm and/or a stricture of right (RHD) or left hepatic duct (LHD), within 2 cm of the bifurcation, of ≤ 1.0 mm^2. Endoscopic treatment (ET) of dominant strictures in PSC could improve clinical parameters [2–7], liver function tests [2–10] and cholangiogram [5,6,11]. Moreover, other studies suggested that ET of DS could improve survival compared with the survival estimated by the Mayo model [2,9,12]. However, cholestatic enzymes may spontaneously fluctuate, without ET, both in patients with and without DS, thus confirming the absence of a unique relationship between the presence of DS and the increase in cholestatic liver enzymes [13]. Moreover, the presence of a severe stricture in CBD did not predict the radiologic progression in patients with PSC over a mean follow-up of 4 years [14]. The incidence of complications of ERCP with or without ET in PSC patients ranges from 4 to 18% in different studies [1] and appears increased compared with the one in patients without PSC [15]. Taken together, all these evidences underline the need to identify criteria for ET in patients with PSC and DS. Magnetic resonance cholangiography (MRC) had substituted ERCP as 1st choice modality for diagnosing PSC due to accuracy and non-invasiveness and it's also recommended prior to ERCP in PSC patients with rapid cholestatic impairment and development of symptoms [16]. Differently from ERCP, MRC lacks hydrostatic pressure and has a lower spatial resolution in the extrahepatic bile ducts (EHBD),

and thus the term dominant strictures cannot be used. At the moment no MRC criteria have proven utility to define strictures that need to be treated and, in clinical practice, a risk-to-benefit evaluation previously to ERCP is recommended [16]. Indeed, if radiological or clinical aggravation of a severe stricture occurred, ERCP is primarily indicated to exclude the presence of cholangiocarcinoma but in case of a stable severe stricture with or without acute clinical indications (acute cholangitis or jaundice), the choice to perform ERCP with ET lacks of objective criteria predictive of improvement after ET. Therefore, the aim of this preliminary study was to investigate radiological and clinical predictive criteria of short-term improvement after dilatation and/or short-term biliary stenting that could be subsequently validated in a multicentre study.

PATIENTS AND METHODS

We included large-duct PSC patients who underwent at least one ERCP with ET for DS preceded by a MRC available for reviewing, in our centre between 2005 and February 2017 with at least 1 year of follow-up after the first ET. Inclusion was defined by the time of first ERCP with ET. Exclusion criteria were the presence of coexisting liver diseases (except overlap with autoimmune hepatitis that were included), recurrent PSC in transplanted patients, decompensated cirrhosis at inclusion, presence of biliodigestive anastomosis, previous or current diagnosis of cholangiocarcinoma or diagnosis of cholangiocarcinoma within 6 months after the inclusion.

MRC technique

Magnetic resonance imaging (MRI) was performed according to the protocol for 3D-MRC in line with the indications given by the International PSC study group [17]. Three radiologists (two senior radiologists, LA (radiologist 1) and SEM (radiologist 2), with 20 and 10 years of experience in MRC and a junior radiologist, EC (radiologist 3), with 2 years of experience, blinded to clinical data, analysed in consensus the closest MRC to ERCP using an interpretation standard model already described [14]. This model includes analysis of the following: intra- (IHBD) and extrahepatic bile duct (EHBD) with regard to strictures, dilatation, and biliary wall enhancement after contrast injection, presence of gallstones, associated liver-related signs including dysmorphy, heterogeneity of liver enhancement after gadolinium-based contrast agents injection, and portal hypertension. Each MRC was also reviewed independently by the three radiologists according to a qualitative score of interpretation (proposed by radiologist 1). This score aimed to evaluate the probability of improvement after ET. The score was as follows: score 3 (improvement likely) was given in case of severe CBD stricture with upstream marked biliary duct dilatation without severe strictures of upstream biliary ducts (Figure 1A), score 1 (improvement unlikely) was given in case of multiple severe strictures of CBD, RHD and LHD and intrahepatic biliary ducts without significant biliary duct dilatation (Figure 1B) and score 2 (improvement undeterminate), was given to an intermediate pattern (Figure 1C). Each MRC was revaluated twice, 6 weeks apart, by radiologist 1 in order to assess intraobserver variability.

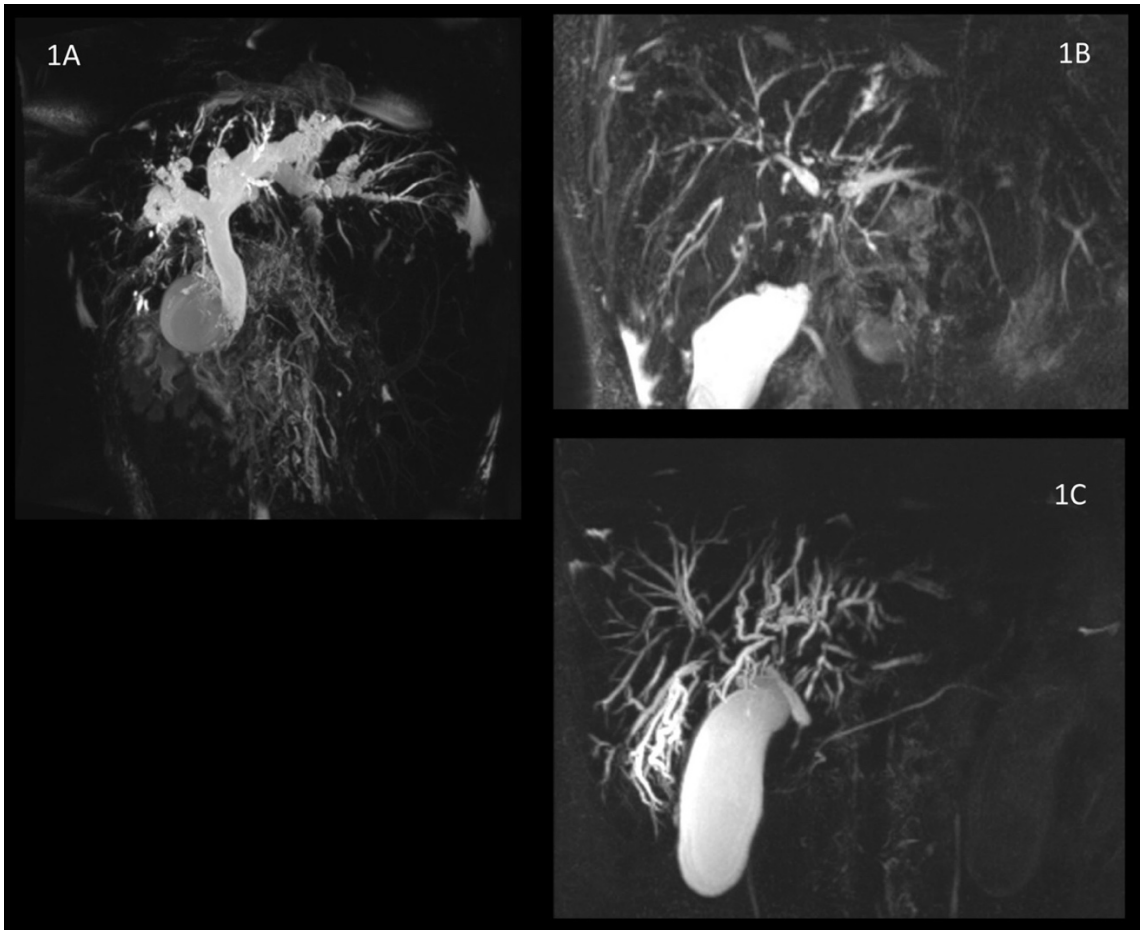
Clinical data

Clinical and biochemical data at inclusion (time of first ERCP with ET), at 2 months after the last ET (time point 2, T2) and at 12 months after the inclusion (time point 12, T12) and details

regarding the type of ET were collected. Failure of the procedure was defined when ET (balloon dilatation +/- stent placement) at second attempt proved impossible.

Response to ET, evaluated in patients without initial failure of the procedure, was assessed at T2 and T12 and was defined by the presence of at least one clinical criterion (resolution of jaundice or acute bacterial cholangitis, resolution or amelioration of right upper abdominal pain or pruritus) or the biochemical criterion (concomitant reduction of at least 40% from baseline values of total bilirubin, alkaline phosphatase and GGT).

Figure 1. Example of qualitative score 3 (improvement likely) (Fig. 1A), score 1 (improvement unlikely) (Fig. 1B), score 2 (improvement undeterminate) (Fig.1C).
Three-dimensional T2 MRC images showing examples of the different scores of improvements. In **Fig.1A** image shows the presence of a severe strictures of lower part of CBD associated to a marked dilatation of upstream CBD, RHD and LHD and intrahepatic biliary ducts characteristic of score 3 (improvement after endoscopic treatment likely). In **Fig. 1B** the presence of multiple severe strictures of CBD, RHD and LHD and intrahepatic biliary ducts and the lack of significant upstream dilatation define the score 1 (improvement after endoscopic treatment unlikely)**. Fig. 1C** demonstrates the presence of severe strictures of CBD, RHD and LHD, intrahepatic biliary ducts with the presence of segments of dilated intrahepatic biliary ducts define the score 2 (improvement undeterminate).



Statistical analysis

Continuous variables were expressed as median and interquartile ranges (IQR: 25th to the 75th percentiles). Dichotomous variables were expressed as number and percentages. Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Quantitative variables were compared using the chi-square test or Fisher's exact test when appropriate to compare features in the two groups (responders vs. non-responders). A difference was considered significant when $p < 0.05$. Univariate analysis and multivariate logistic regression analysis were

performed to identify predictive factors of response to ET at the two time points. The multivariate analysis included variables found significant in the univariate analysis. Continuous variables were included after dichotomisation in binomial variables using median values as cutoff. Radiological variables were categorized in binomial variables according to presence or absence of the most severe feature. Intraobserver variability was evaluated using Cohen's κ coefficient [18] and interobserver variability was evaluated using Fleiss' κ coefficient [19]. Interpretation of the kappa values was performed according to the guidelines of Landis and Koch [20] with kappa values > 0.8 considered excellent agreement, 0.79 to 0.60 substantial, 0.59 to 0.40 moderate, 0.39 to 0.20 slight and < 0.20 poor agreement.

RESULTS

We included 31 PSC patients who underwent at least one ERCP with ET for dominant strictures preceded by a MRC. All patients had intra- and extrahepatic bile ducts PSC localization, and all patients were treated with ursodeoxycholic acid. Clinical and biochemical characteristics are reported in Table 1. Half of patients (n=15) had acute cholangitis or jaundice at the time of inclusion.

Table 1. Patients' characteristics at inclusion

Characteristics	
Male gender, n(%)	20(65)
Age at inclusion	36(27-52)
Cirrhosis	10(32%)
Acute cholangitis	5(16%)
Jaundice	15(48%)
Pruritus	12(39%)
Right upper abdominal pain	7(23%)
Total bilirubin (μmol/L)	35(17-89)
ALP (N.R. 43–115 U/L)	262(174-379)
AST (N.R. 10-35 U/L)	72 (47-141)
GGT (N.R. 3-45 U/L)	227(94-345)
PT (N.R. 75-112%)	91(69-100)

Abbreviations: ALP, Alkaline phosphatase, N.R., normal range, AST, aspartate aminotransferase, GGT, gamma glutamyl transpeptidase, PT, prothrombin time

MRI findings

Mean interval time between MRI and ERCP was 79 ± 71 days. Radiologic findings found at MRI at inclusion are reported in Table 2. All patients had a severe CBD stricture (>75%) that was associated to an upstream dilatation in 20% of patients. Seventy-one percent and 54% of patients had a severe stricture in RHD and LHD. All patients had strictures located in more than 25% of IHBD and severe IHBD strictures were present in all but one patients and the majority of them had moderate to marked IHBD dilatation. A quarter of patients presented intraductal stones. Dysmorphy and signs of portal hypertension were observed in 74% and 29% of patients respectively. IHBD or EHBD enhancement after gadolinium based contrast agent injection was present in around 40% of patients.

According to the qualitative score of improvement evaluated by radiologist 1 at first evaluation seven patients were judged unlikely (score 1) to improve after ET, sixteen patients were judged likely (score 3) and finally nine patients had an indeterminate pattern of improvement (score 2). Intraobserver variability between repeated evaluations by radiologist 1 was 74%, k = 0.6 indicating substantial agreement. Interobserver variability of the qualitative score of improvement between the three radiologists was 60%, k = 0.40, indicating fair agreement.

Table 2. Radiologic findings at inclusion MRI in 31 PSC patients before endoscopic treatment.

Features	PSC patients (n.31)
CBD strictures	
Absent	-
≤75%	-
>75%	31(100%)
CBD stricture length	
≤2 mm	2(7%)
3-10 mm	5(16%)
>10 mm	24(77%)
CBD dilatation	
≤10 mm	25(81%)
11-14 mm	2(6%)
≥15 mm	4(13%)
CBD enhancement	
Absent	14(61%)
Thickness <2 mm	6(26%)
Thickness 2-6 mm	3(13%)
Thickness >6 mm	-
RHD strictures	
Absent	7(23%)
≤75%	2(6%)
>75%	22(71%)
RHD stricture length	
Absent	7(23%)
≤2 mm	3(10%)
3-10 mm	10(32%)
>10 mm	11(35%)
RHD dilatation	
≤6 mm	20(65%)
7-8 mm	5(16%)
≥9 mm	6(19%)
RHD enhancement	
Absent	14(61%)
Thickness <2mm	6(26%)
Thickness 2-6 mm	3(13%)
Thickness >6 mm	0
LHD strictures	
Absent	7(23%)
≤75%	7(23%)
>75%	17(54%)
LHD stricture length	
Absent	7(23%)
≤2 mm	3(10%)
3-10 mm	14(45%)
>10 mm	7(23%)
LHD dilatation	
≤6 mm	20(65%)
7-8 mm	3(10%)
≥9 mm	8(25%)
LHD enhancement	
Absent	14(61%)
Thickness <2mm	6(26%)
Thickness 2-6 mm	3(13%)
Thickness >6 mm	-
IHBD Stricture	
Absent	-
≤75%	1(3%)
>75%	30 (97%)
IHBD involvement	
absent	-
≤25%	-
>25%	31(100%)
IHBD dilatation	
None (≤3 mm)	5(16%)
mild (4 mm)	16(52%)
marked (≥5 mm)	10(32%)
IHBD enhancement:	
Absent	15(65%)
thickness <2mm	5(22%)
thickness 2-6 mm	3(13%)
thickness>6 mm	-
Intraductal stones	
Absent	23(74%)
Present	8(26%)
Dysmorphy	
Absent	8(26%)
Present	23(74%)
Portal Hypertension	
Absent	22(71%)
Present	9(29%)
Parenchymal enhancement heterogeneity	
Absent	1(4%)
Present	22(96%)

Endoscopic interventions

According local policy, all PSC patients followed-up in our centre were monitored by annual MRC. Moreover, in case of biochemical aggravation, a new MRC was performed. The decision to perform an ERCP with ET, made by a multidisciplinary staff, was based on the presence of a severe stricture in the CBD or RHD and/or LHD, found at MRC, associated to radiologic progression, clinical or biochemical worsening. Multidisciplinary staff evaluated risk to benefit of ET case-by-case. A dominant stricture in CBD was confirmed by ERCP in all patients. A single DS stricture localized in CBD was observed in seventeen patients, otherwise DS in both CBD and RHD were found in three patients and finally, seven patients had multiple DS localized in CBD, RHD and LHD. Four patients had a DS in CBD associated to intraductal stones. The majority of patients underwent sphincterotomy with balloon dilatation and stent placement and technical success of was obtained in 27 patients at first ERCP, in 3 patients at second ERCP and 1 patient had a technical failure (failure to pass the stricture). Most of patients needed a second ERCP within a median time of 41 days from the first ERCP to complete the dilatation or to remove biliary stent. Brush cytology was obtained in each patient without initial failure and the presence of neoplastic cells was excluded in all cases. Subsequent clinical and radiological follow-up confirmed the benign nature of the DS.

Seven (11%) post-procedure complications were observed in seven (22%) patients, three of them developed post-ERCP acute pancreatitis, one patient developed biliary peritonitis with subsequent cholecystectomy and two patients had post sphincterotomy gastrointestinal bleeding, finally one patient had a post-ERCP duodenal perforation. A history of one or more acute cholangitis after the first ERCP was observed in nineteen patients, of them one was transplanted within 12 months from first ERCP for recurrent acute cholangitis and one patient developed cirrhotic decompensation.

Evaluation of response to ERCP

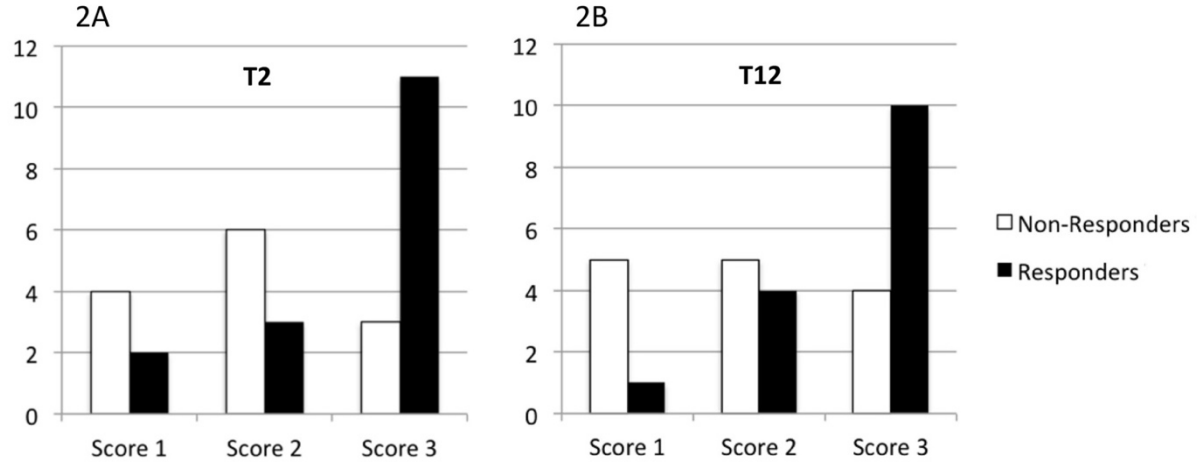
Response to ET was observed in sixteen (53%) patients at T2 and in fifteen (50%) patients at T12. In the total cohort, a significant improvement of total bilirubin and aspartate aminotransferase was observed at end of follow up [35(17-89) *vs.* 16(11-28) μmol/L p<0.01 and 72(47-141) *vs.* 54(28-89) U/L, p=0.03, respectively].

Responders at T2 were characterized, at inclusion, by significantly higher total bilirubin [63(33-171) vs. 23(12-62), p= 0.03], AST [105(69-211) vs. 52(39-89) U/L, p=0.01] and ALP serum levels [356(208-565) vs. 203(153-271) U/L, p=0.02], lower prothrombin time [82(66-94) vs. 99(89-110), p=0.01], a higher frequency of pruritus and upper right abdominal pain (63% vs. 8%, p<0.01 and 44% vs. 0%, p=0.01, respectively), a higher frequency of severe (≥ 9 mm) LHD dilatations and short (≤ 10 mm) LHD stricture (44% vs. 8%, p=0.04 and 94% vs. 54%, p=0.03, respectively) compared to T2 non-responders. At univariate analysis, variables significantly associated with response to ET at T2 were the presence of pruritus, total bilirubin, AST, ALP, the presence of short LHD strictures and severe LHD dilatation (data not shown). Independent predictors of response at T2 identified at multivariate analysis were the presence of short LHD stricture (HR 24, 95%CI 1.3-464.8, p=0.03) and AST (HR 27, 95%CI 2-362, p=0.01).

Responders at T12 were characterized, at inclusion, by higher AST serum level (113(72-225) vs. 53(41-68), p<0.01), higher bilirubin (75(51-172) vs. 20(12-30), p=0.02), lower PT (87(65-99) vs. 98(89-109), p=0.03) higher frequency of pruritus (67% vs. 7%, p<0.01) and severe CBD dilatations (27% vs. 0, p=0.05), short (≤ 10 mm) LHD strictures (93% vs. 57%, p=0.04) and qualitative score 3 (67% vs. 29%, p = 0.05). At univariate analysis, total bilirubin, AST, presence of pruritus, short LHD strictures and qualitative score 3 (Figure 2) were associated to response at T12 (data not shown). At multivariate analysis total bilirubin and AST at inclusion were

independent predictive factors of response at T12 (*HR* 19.1, 95%CI: 1.7-221.8, p=0.02 and HR 18.8, 95%CI: 1.6-222, p=0.02).

Figure2. Distribution of responders and non-responder to endoscopic treatment at 2 months (T2) (Fig.2A) and 12 months (T12) after endoscopic treatment (Fig.2B) according the qualitative score of improvement at baseline.



DISCUSSION

This is the first study that aims to identify MRC and clinical criteria able to predict improvement after ET in PSC patients with severe extrahepatic bile duct strictures. We included a cohort of large-duct PSC patients followed-up in a single centre and we evaluated radiological and clinical features before ET of the stricture. We used a standard model of MRC interpretation of PSC features [14] and we found that, at inclusion, a severe stricture of CBD (reduction of at least 75% of the diameter of the duct) was present in all treated patients. Moreover, half of them had also a severe stricture of RHD and/or LHD.

We evaluated the difference between responders and non-responders and we observed that 12-months responders were characterized, at inclusion, by a more active and symptomatic disease with more frequent marked CBD dilatation, short LHD strictures and qualitative score

3 even if total bilirubin and transaminase were the only two independent predictors of response at multivariate analysis. Thus, we observed that a better response to ET is achieved in patients with evident clinical manifestation and probably in patients with severe dilatation in CBD and short LHD stricture but further conclusions could not be derived and this is at least in part due to the small number of cases that limited the statistical power of the study.

Recently Zenouzi *et al.* described a number of relevant points regarding the real-life interpretation of MRC in PSC patients and reported observation which differ from our results [21]. First, interobserver agreement between experts regarding the decision to perform endoscopic treatment in case of significant strictures was poor (k=0.12) [21] and it resulted lower compared with the interobserver agreement of the qualitative score of improvement (k=0.40) reported in our study. One of the reasons could be the different expertise among physicians (hepatologist, gastroenterologist and radiologist) involved in the interpretation of clinical and radiological PSC clinical cases [21]. Moreover, they observed that a high total bilirubin and the presence of acute cholangitis were the main reasons to indicate the ET. Differently, in our cohort, only half of patients had jaundice or acute cholangitis. Finally, they observed that there was no concordance between *a priori* probability of improvement, in other words expert's indication to perform ET, and the observed results of the procedure [21]. All together, these data confirm the need in clinical practice of objective criteria able to predict the improvement after ET, particularly in patients with severe stricture but without a clear clinical indication (jaundice or acute cholangitis). Indeed, a short term improvement after ET, of symptoms and biochemistry was recently reported in 77% of patients with DS and without acute cholangitis [22]. Moreover, efficacy of balloon dilatation and short-term stenting were similar in term of recurrence free-survival, improvement of symptoms and cholestatic enzymes [22].

In the current study, we defined an arbitrary criterion of response to ET that evaluates clinical and biochemical but not radiological response similarly to what has been previously proposed [23]. Here, the biochemical criterion was defined as an improvement of three liver enzymes (bilirubin, GGT, ALP) in order to reduce the probability that a spontaneous fluctuation of liver enzymes could be interpreted as a biochemical response.

One limitation of our study is the rather short follow-up (12 months) letting unresolved the question of the long-term efficacy of ET notably in term of transplant-free survival. Another limitation that we could overcome by expanding the study cohort is the lack of adjustment for different factors (reason for ERCP, technical failure at first ERCP, complications, age, number of ERCP after the first), for number and localization of strictures (only CBD vs. CBD + RHD or LHD) and for the type of endoscopic treatment (simple balloon dilatation vs. short term stenting).

Initial technical failure, in the current study, was reported in 3.2% of patients, that is comparable to the recent data of DILSTENT trial (5%) [22] and finally, moderate to severe complications developed after 11% of procedures, similarly to what previously described (1), confirming that risk to benefit evaluation of ET should be always discussed and the research of non-invasive predictive criteria of response is a major need in these patients.

In conclusion, in PSC patients with severe strictures of extrahepatic bile duct, MRC may contribute to identify patients likely to benefit from ET as well as biochemical features. A validation in a larger cohort is warranted to confirm these results, especially in patients without a clear indication to ET.

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CHAPTER 11

General conclusion and future perspectives

Nora Cazzagon

GENERAL CONCLUSION AND FUTURE PERSPECTIVES

In this thesis I discussed previous results regarding the current knowledge on the use of MRC in PSC and I described the possible application of this technique in the follow-up of these patients.

Indeed, I assessed the prognostic value of two simple magnetic risk scores, depending on gadolinium-based contrast agent administration, in prediction the risk of developing adverse outcome in a large population of PSC patients and then I validated the results in an external multicentric international cohort. Then, I demonstrated that the use in combination of the magnetic resonance risk score without contrast injection with liver stiffness improves risk stratification in patients with PSC and I identified three subgroups with different risk and survival.

These first two studies provide evidences to sustain the use of magnetic resonance cholangiography for risk stratification of PSC patients. This could be applied to identify new management strategies according different risk subgroups and to better select patients for clinical trials.

Future research in this field should confirm these results in external cohort of PSC patients and report on the applicability of the standard model of interpretation by radiologists of other centers.

I then reported on a group of PSC patients characterized by the presence of intrahepatic bile duct cystic dilatations and I demonstrated that this group appeared clinically and radiologically distinct from the classical large duct PSC and it is characterized by a worst prognosis. I proposed some pathogenetic hypothesis regarding cystic dilatation development and a

project to explore one of this possible mechanism is now under development in collaboration with scientists of the Hamburg-Eppendorf University.

The fourth study is a research of predictive factors of response to endoscopic treatment for severe stenosis in patients with PSC based on magnetic resonance and clinical findings. I here proposed a criterion of response, a new qualitative score of possible improvement based on a pictorial description of MRI findings and I suggests a possible role of MRI to select candidates to endoscopic treatment. Clearly, due to the small sample size, I was unable to provide evident conclusions and for this reason, this project has been proposed in June 2018 to the other members of the MRI working group at IPSCSG Biannual meeting held in Paris.

Two centers of two different European countries are now collecting data and other centers agreed to participate.

In conclusion, I here provided some evidences in favour of the use of magnetic resonance imaging for prognostic other than diagnostic purposes in PSC. I strongly believe that the wide use of MRI in PSC patients in different centers and the increasing integration of radiological with clinical semiology of the disease will improve the knowledge of the disease course and would provide new insights for future basic research into disease aetiology and pathogenesis.