REVIEW

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Inflammatory Bowel Disease and Primary Sclerosing Cholangitis: A Review of the Phenotype and Associated Specific Features

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Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic disease that is associated with inflammatory bowel disease (IBD) in approximately 70% of cases. Although the pathogenesis is still unknown for both diseases, there is increasing evidence to indicate that they share a common underlying predisposition. Herein, we review the epidemiology, diagnosis, disease pathogenesis, and specific clinical features of the PSC-IBD phenotype. Patients with PSC-IBD have a distinct IBD phenotype with an increased incidence of pancolitis, backwash ileitis, and rectal sparing. Despite often having extensive colonic involvement, these patients present with mild intestinal symptoms or are even asymptomatic, which can delay the diagnosis of IBD. Although the IBD phenotype has been well characterized in PSC patients, the natural history and disease behavior of PSC in PSC-IBD patients is less well defined. There is conflicting evidence regarding the course of IBD in PSC-IBD patients who receive liver transplantation and their risk of recurrent PSC. IBD may also be associated with an increased risk of cholangiocarcinoma in PSC patients. Overall, the PSC-IBD population has an increased risk of developing colorectal neoplasia compared to the conventional IBD population. Lifelong annual surveillance colonoscopy is currently recommended. **(Gut Liver 2018;12:17-29)**

Key Words: Inflammatory bowel disease; Cholangitis, sclerosing; Diagnosis; Liver transplantation; Colorectal neoplasms

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease of the gastrointestinal tract. Up to 50% of patients may develop extraintestinal manifestations (EIM) during their disease course.[1] One such EIM is primary sclerosing cholangitis (PSC), described for the first time in 1965.[2] PSC is a chronic and progressive cholestatic disease, characterized by inflammation and fibrosis of the intrahepatic and/or extrahepatic ducts,[3] that may result in liver cirrhosis and eventually end-stage liver disease.[3] Orthotopic liver transplantation (OLT) is the only potentially curative therapy for PSC, with survival rates of 85% and 70% at 5 and 10 years, respectively.[3] Without OLT, half of symptomatic patients die within 12 to 15 years.

In Western countries, the reported incidence of PSC is 0.07 to 1.3 per 10^5/yr, and the prevalence is 8.5 to 13.6 per 10^5.[4,5] About 70% of patients with PSC have underlying IBD, most frequently ulcerative colitis (UC) in over 75% of cases.[6] The prevalence of IBD in PSC patients ranges from 50% to 99% across different studies.[6] Several factors could explain this large variation. In a recent systematic review, the studies that used both endoscopic and histological criteria for IBD diagnosis, showed a higher median percentage of IBD among PSC patients.[6] Geographic differences could also contribute to this variation. Asian studies report a lower prevalence of IBD in PSC patients in comparison to European and American populations.[7,8] However, in some of these studies, IBD diagnosis was established or excluded based on registry data or notes in medical files without reviewing original endoscopy or histology. In fact, a recent Japanese report by Sano *et al*.[9] using strict case ascertainment criteria reported an IBD incidence of 68.9% among PSC patients. Since disease activity of IBD in PSC patients is often mild and occasionally asymptomatic, it is important to assure the use of endoscopic and histological criteria when assessing IBD incidence in this population. Conversely, in patients with known IBD, PSC is found much less commonly, occurring in about 2% to 8% of UC patients and 3% of Crohn's disease (CD) cases.[6]

Although there may be a possible common pathogenesis

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between PSC and IBD, the two disorders can occur at different times. PSC may be diagnosed many years after proctocolectomy for colitis, and conversely IBD can appear many years after the initial diagnosis of PSC or even after OLT altogether.[10] In most reports, IBD diagnosis precedes that of PSC.[11,12] In a recent report, Sinakos *et al*.[13] demonstrated an increased frequency of PSC being diagnosed first when comparing two time cohorts (35% in 1993–1997 vs 50% in 2003–2007, p=0.0009). An inherent bias in determining the timing of diagnosis pertains to the fact that PSC may have a silent asymptomatic period, and equally the IBD associated with PSC may be mildly symptomatic or even asymptomatic, and therefore can go underdiagnosed. Since 70% of PSC cases are associated with IBD, the presence of CD or UC makes the diagnosis of PSC easier.[3] In patients with known IBD, the presence of persistent unexplained cholestasis obliges one to exclude concurrent PSC through magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography, especially if the patient is symptomatic for biliary obstruction. When PSC is diagnosed first, half of the cases have only abnormal laboratory tests; the typical diagnostic hallmarks of fever, itching, and jaundice are rarely seen nowadays.[3] Symptomatic patients usually present with fatigue and pruritus and can also exhibit jaundice, hepatosplenomegaly or scratching injuries. Recurrent episodes of bacterial cholangitis with fevers, chills, right upper quadrant pain and jaundice can also be a part of the clinical presentation, and usually develops in about 10% to 15% of patients during the course of the disease.[14] The diagnosis of PSC is based on the findings of diffuse multifocal strictures and dilations in the intrahepatic and/or extrahepatic biliary tree.[3] Patients with a confirmed diagnosis of PSC should undergo colonoscopy with biopsies to exclude concomitant IBD or any malignancy,[3] even if they report no gastrointestinal symptoms. As the majority of PSC-IBD patients have mild disease activity and even possible normal endoscopic appearances, histological sampling is crucial to avoid underdiagnosis.[6] Although no evidence-based guidelines are available, if the index colonoscopy is negative for IBD, a repeat colonoscopy every 3 to 5 years should be performed to monitor for possible onset of IBD.[15]

DISEASE PATHOGENESIS

PSC is likely to have an underlying multifactorial etiology, with a predominant immune-mediated process.[3] PSC and IBD are interrelated conditions that may well share an underlying predisposition (Fig. 1). Both diseases share common antibodies, such as those directed against cytoplasmic and nuclear antigens of neutrophils with a characteristic perinuclear staining pattern (p-ANCA). p-ANCA antibodies have been found in 26% to 85% of PSC patients and in up to 68% of patients with UC.[3]

From a genetic standpoint there is increasing evidence that PSC is distinct from UC and CD. Large-scale genome-wide association studies (GWAS) have identified close to 200 independent loci associated with IBD.[16,17] Most of these loci are shared between UC and CD.[16] GWAS studies in PSC have identified a total of 16 PSC susceptibility loci.[18] In the most recent genetic analysis there was surprisingly limited overlap between PSC and IBD loci.[19] Half of the PSC loci failed to show a robust association with IBD, suggesting overlapping yet distinct genetic mechanisms.[19] Genetic predisposition to autoimmune bile duct injury triggered by toxic or infectious agents that may gain access through the diseased colon is potentially a major mechanism leading to PSC in IBD patients.

Two hypotheses that link PSC and IBD include the "gut lym-

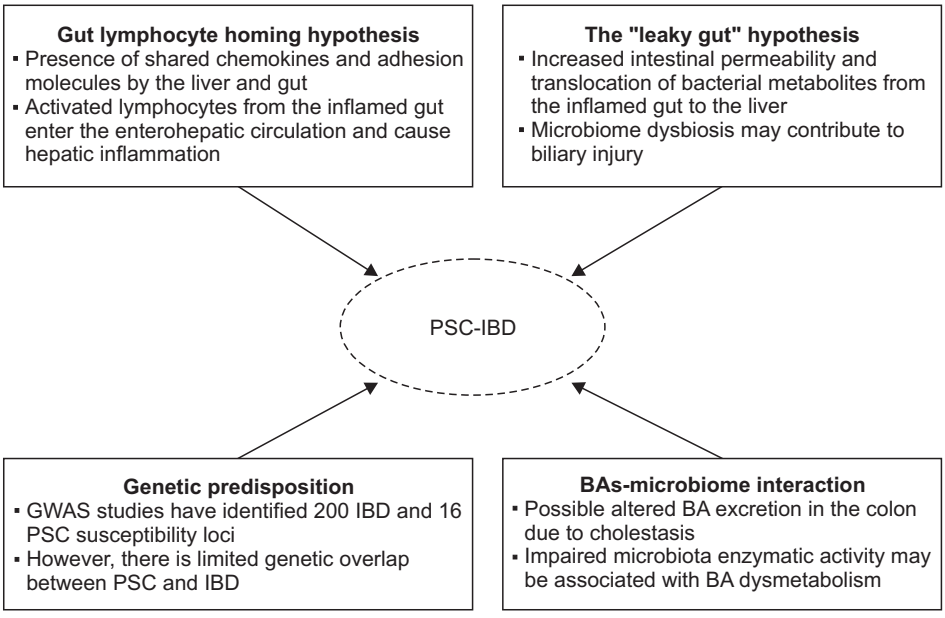

Fig. 1. Possible hypothesis linking primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) pathogenesis, including the genetic predisposition, immune-mediated processes, altered gut microbiota and altered bile acid (BA) metabolism.
GWAS, genome-wide association studies.

phocyte homing" hypothesis and the "leaky gut" hypothesis.[20] Activated lymphocytes from the inflamed and permeable gut may enter the enterohepatic circulation and persist as memory cells that cause hepatic inflammation.[21,22] Some molecular features, such as chemokines and adhesion molecules, are shared by the liver and intestine and could contribute to lymphocyte binding at both sites.[21] T cells activated in the gut during active IBD could differentiate into effector cells with the ability to bind to both hepatic and mucosal endothelium. The activation and expansion of these memory cells in the liver could eventually lead to the induction of MAdCAM-1 and CCL25 in the liver, promoting the recruitment of $CCR9^+$ $\alpha4\beta7^+$ mucosal T cells and the development of inflammation.[23] Findings such as PSC development after colectomy for IBD, or the development of IBD after OLT for PSC, have led some investigators to suggest that aberrant homing of lymphocytes between the intestine and liver could be involved in the pathogenesis of the PSC-IBD phenotype.[21]

The "leaky gut" hypothesis refers to the association between progressive hepatic and biliary injury and increased intestinal permeability and translocation of bacterial metabolites from the gut.[24] The liver receives approximately 75% of its blood supply from the splanchnic circulation and is constantly exposed to both beneficial and noxious molecules from the intestinal microbiome.[25] This so-called "gut-liver axis" is essential for the maintenance of health but may also play an important role in pathogenesis of liver and intestinal diseases.[25,26] In IBD there is a known intestinal microbiome dysbiosis, characterized by lower biodiversity and decreased bacteria of the *Firmicutes* phylum.[27] In PSC-IBD patients there is also an altered microbiome composition, and it appears to be different from IBD-only patients.[28,29] Recent evidence suggests a marked increase in *Veillonella*, *Escherichia*, *Lachnospiraceae* and *Megasphera* genera in PSC-IBD patients.[28,29] Other genus such as *Prevotella*, *Roseburia*, and *Bacteroides* are significantly reduced.[28] This dysbiosis may be associated with mucosal immunity dysregulation by modulating intestinal permeability and altering homing of gut-specific lymphocytes.[28] Recently, evidence for an etiologic role of the intestinal microbiome in PSC has been provided by animal model studies. Tabibian *et al*.[30] used MDR2 knockout mice (a widely utilized animal model of PSC) to assess the role of the commensal microbiota in the pathogenesis of biliary injury. Germ-free MDR2 knockout mice exhibited a dramatically worsened PSC phenotype, with exacerbated biochemical and histological features and an increase in cholangiocyte senescence.[30] Additionally the authors found that ursodeoxycholic acid (UDCA), which is a commensal microbial metabolite, had an antisenescent effect in an *in vitro* model.[30] These findings demonstrate the protective role of commensal microbiota and its metabolites against biliary injury and hint at possible new targets for future studies of therapeutic interventions in PSC.

The interaction between microbiota and bile acid (BA) metabolism may also play an important role in the PSC-IBD phenotype. Recent evidence supports the existence of BA dysmetabolism in IBD patients due to impaired microbiota enzymatic activity.[27] One of the contributing factors for the difference in phenotype between PSC-IBD patients and IBD controls may be altered concentration and/or composition of colonic BA impacting on gut microbiota and stool BA metabolism.

In summary, PSC-IBD pathogenesis is still unclear but this phenotype is likely to have an underlying multifactorial etiology, influenced by genetic predisposition, immune-mediated processes and altered gut microbiota (Fig. 1).

CLINICAL FEATURES OF PSC-IBD

1. Demographic features of patients with PSC-IBD

Patients with the PSC-IBD phenotype have demographic features resembling PSC cases, although the PSC diagnosis tends to occur at a younger age, when compared with PSC-only controls (mean age, 33.6±17.2 years vs 58.9±18.2 years; $p<0.001$).[9] The incidence is higher in males and is more prevalent in young and middle-aged patients.[13-15] The age at clinical onset of IBD is controversial. Some reports indicate that the mean age for IBD diagnosis is higher among PSC-IBD patients compared with IBD controls,[15] but a recent study reported that PSC-UC patients had a UC diagnosis at a significantly earlier age compared with UC controls (mean age, 24.5 years vs 33.8 years).[31]

2. The IBD phenotype of PSC-IBD patients

As stated above, the co-occurrence of PSC with IBD is associated with a distinct IBD phenotype (Fig. 2). PSC-IBD patients typically have mild intestinal disease activity and an increased incidence of extensive colitis and pancolitis, rectal sparing and

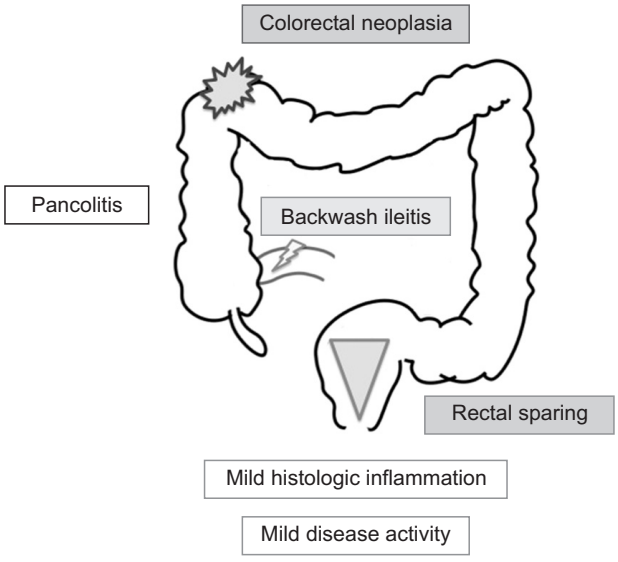

Fig. 2. Phenotypic features of primary sclerosing cholangitis and inflammatory bowel disease.

backwash ileitis (Table 1).[9,10,12,13,15,31-38] Extensive colonic involvement, irrespective of the IBD subtype (i.e., CD vs UC), is the primary IBD phenotype associated with PSC. From a population-based cohort of 579 PSC patients in the Netherlands, pancolitis was observed in 94% of PSC-UC patients and in 96% of PSC-CD patients.[37] Though rare, some patients with ulcerative proctitis and Crohn's ileitis have concomitant PSC.[37,39] Although pancolitis is a characteristic finding of PSC-IBD patients, it occurs at variable rates (35% to 95% of patients).[6] Some cases are endoscopically diagnosed as right-sided IBD.[11] In a recent systematic review, the majority of studies addressing disease activity found that the prevalence of inflammation was highest in the right colon and lowest toward the distal colon.[6,9,12] This pattern of inflammation was significantly different from matched non-PSC IBD-controls.[6,9,12]

The frequency of rectal sparing and backwash ileitis in PSC-UC patients differs among reports. A recent systematic review reported an incidence of rectal sparing from 6% to 66% (versus 2% to 25% in IBD without PSC) and of backwash ileitis between 5% and 46% (compared to 3% to 24% in UC without PSC).[6] It is worth noting that since PSC-IBD patients typically have quiescent disease, microscopic inflammation may still be present in spite of an endoscopically normal-appearing rectum.[12] The frequency of rectal sparing and backwash ileitis should be investigated in future studies using a consensus definition.

In PSC-CD patients, the anatomic location of the disease differs from patients with isolated CD. Colonic involvement is the most often reported (37% to 82%), followed by ileocolic involvement (22% to 58%), and rarely isolated ileal involvement (2% to 5%).[6] In PSC-CD patients there is a lower frequency of stricturing and penetrating disease compared to patients with isolated CD.[6,39]

3. IBD disease activity in PSC-IBD patients

Despite the higher prevalence of pancolitis, the intestinal inflammation in PSC-IBD patients is usually quiescent leading to mild symptoms, reduced use of steroids and decreased rates of hospitalization.[9,10] On histological grounds, the colonic inflammation is also very mild, with only focal basal plasmacytosis and occasional mild cryptitis.[10] Schaeffer *et al*.[10] reported histological findings of 97 PSC-IBD patients and found no evidence of severe disease activity (active cryptitis with crypt abscesses, surface erosion or ulceration) in any of the patients. In a matched case-control study by Joo *et al*.,[31] PSC-UC patients demonstrated an overall significantly lower grade of inflammation in the colon compared with UC controls (mean grade, 2.09 ± 0.085 vs 2.59 ± 0.92; $p<0.05$). Furthermore, there are some data to suggest that there is an inverse relationship between PSC disease severity and IBD activity. Marelli *et al*.[35] evaluated 96 patients with PSC-UC, 52% of whom needed OLT for worsening PSC, and compared them with the PSC-IBD group that did not need OLT. The PSC-IBD group that needed OLT more frequently had clinically quiescent UC, fewer UC flares, and required less steroids and immunosuppressives. By contrast, the group where OLT was not performed showed an increased need for intestinal surgery and more frequent colorectal neoplasia (CRN).[35] These data suggest that PSC severity may have a "protective" effect on UC's activity.

4. Course of IBD after OLT

There is conflicting evidence regarding the course of IBD after OLT for PSC. Several reports demonstrated worsening

Table 1. Studies Evaluating IBD Extension, Backwash Ileitis, and Spared Rectum in PSC-IBD Patients Compared to IBD-Only Controls

Study	Year	No. of patients		IBD extension (proctitis/left-sided/pancolitis) %		Backwash ileitis %		Rectal sparing %	
		PSC-IBD	IBD	PSC-IBD	IBD	PSC-IBD	IBD	PSC-IBD	IBD
Olsson *et al*.[32]	1991	55	1,445	5.5/NA/94.5	38.2/NA/61.8	NA	NA	NA	NA
Loftus *et al*.[15]	2005	71	142	NA/NA/87	NA/NA/54	51	7	52	6
Sokol *et al*.[33]	2008	75	150	NA	NA	18.7	24	20	13.3
Joo *et al*.[31]	2009	40	40	0/7.5/85	0/35/45	10	7.5	27.5	25
Sano *et al*.[9]	2011	20	60	5/5/35	30/31.7/35	NA	NA	NA	NA
Ye *et al*.[34]	2011	21	63	NA/NA/95.2	NA/NA/55.6	42.9	3.2	38.1	1.6
Marelli *et al*.[35]	2011	96	0	0/10/90	NA	NA	NA	NA	NA
Jorgensen *et al*.[12]	2012	110	0	NA/3/55	NA	20	NA	65	NA
O'Toole *et al*.[36]	2012	103	2,649	1/22.3/54.4	7.9/24.5/25	NA	NA	NA	NA
Boonstra *et al*.[37]	2012	80	80	2.5/2.5/65	5/20/43.8	5	2.5	10	1.3
Gelley *et al*.[38]	2012	20	0	15/15/55	NA	NA	NA	NA	NA
Schaeffer *et al*.[10]	2013	97	0	0/17.5/43.4	NA	NA	NA	NA	NA
Sinakos *et al*.[13]	2013	129	0	NA/12.4/58.9	NA	11.6	NA	24	NA

IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; NA, not available.

colitis activity following OLT in approximately 30% of PSC-IBD patients.[3] Furthermore, de-novo IBD after OLT has also been reported and it may develop in 14% to 30% of PSC patients up to 10 years after transplantation.[40] Retrospective studies comparing IBD activity before and after liver transplantation found that endoscopic colonic inflammation was more frequent after OLT, as was the rate of relapse and overall clinical IBD activity.[41,42] A retrospective study of 31 patients with PSC-UC who received OLT, showed that the Mayo score was higher after transplantation compared with the pre-transplant score (mean score, 2.91±0.9 vs 6.64±3.7; p=0.009).[38] The above findings have led to the speculation that the diseased PSC liver somehow keeps colonic inflammation in check. Several factors may be associated with a worse course of IBD after OLT such as a new balance in the immune system favoring an immune-mediated attack against the colonic mucosa, the presence of active IBD at the time of transplantation, discontinuation of 5-aminosalicylates, infrequent use of azathioprine and the use of tacrolimus.[35,42] Haagsma *et al*.[43] proposed that patients treated with tacrolimus had a stronger suppression of interleukin-2 production by T-cells and that resulted in an inability to activate regulatory responses. However, subsequent studies did not confirm this suggestion.[41,44] Although further studies are required, cyclosporine and azathioprine are preferred over tacrolimus because they seem to have a more favorable outcome on IBD after OLT for PSC.[6] Anti-tumor necrosis factor treatment may also be effective and safe for treating IBD in this context.[3] Early colectomy should be considered for patients with severe colonic inflammation after OLT.[38] A recent systematic review, reported a colectomy rate after OLT ranging from 4% to 20%.[6]

Of note, the worsening of IBD after OLT has not been universally confirmed. Jorgensen *et al*.[12] performed a cross-sectional study in 155 PSC-IBD patients. Forty-two patients (38%) had undergone OLT and had a lower clinical and histologic disease activity when compared to the nontransplanted cohort. The authors suggested this could be due to the implementation of immunosuppressive medication in the transplanted group, namely long-term prednisolone therapy that may be a predictor of less severe IBD posttransplant.[12]

5. Course of IBD after proctocolectomy

PSC-IBD patients who undergo proctocolectomy with ileal pouch anal anastomosis (IPAA) have a higher risk of developing pouchitis, which affects 13.8% to 90% of cases (versus 33% in patients with conventional IBD).[6,13,15] Nonetheless, the long-term outcomes are often satisfactory,[45] with the incidence of pouch failure in PSC-IBD patients subjected to IPAA being similar to IBD-only patients.[6] Mathis *et al*.[45] reported retrospectively on 100 patients with PSC-UC who underwent IPAA with 6 years of follow-up. Pouch failure was observed in only 3% of patients due to refractory pouchitis, pouch cancer or fistula formation.[45] The mechanism underlying the association between PSC and pouchitis remains unclear.

6. The PSC phenotype of PSC-IBD patients

While PSC is often associated with a distinctive IBD phenotype,[35] the effect of IBD on the natural history and disease behavior of PSC is less well defined. In PSC patients with concomitant IBD, the PSC phenotype may differ when compared to PSC patients without IBD. Combined intrahepatic and extrahepatic biliary involvement has been described to be more common in PSC-IBD patients compared to PSC patients alone (81.5% vs 46.2%, p<0.05),[46] but has not always been described in the literature. At least two other retrospective reviews have refuted the finding of a higher prevalence of intra- and extra-hepatic biliary involvement in patients with coexisting IBD.[47,48]

Long-term PSC outcomes also do not seem to be associated with the presence or disease severity of IBD. In a natural history study of 305 Swedish PSC patients, associated IBD had no prognostic significance on the need for OLT or liver-related deaths.[49] Similarly, transplant-free survival rates, cirrhosis rates, and mortality of PSC patients were found to be independent of concomitant IBD in a retrospective Israeli study of 141 PSC patients.[48] Navaneethan *et al*.[47] also concluded that UC did not affect the long-term liver outcomes in PSC patients including death or need for OLT, after controlling for liver disease severity. As corroborative evidence to this study, Ludwig *et al*.[50] found that there were no significant histological differences including periductal fibrosis, periductal inflammation, portal edema and fibrosis or cholestasis between PSC patients and PSC-UC patients on liver biopsy specimens. Nevertheless, in a population-based epidemiologic study of PSC patients from New Zealand, PSC-IBD patients when compared to PSC patients were more likely to require OLT or die (p=0.03).[51]

In contrast to the majority of findings reported in the aforementioned studies, some of the PSC-IBD literature suggests that the rapidity of PSC disease progression may be contingent upon the specific IBD phenotype. A retrospective case-controlled study utilizing the Oxford PSC and IBD databases revealed that major event-free survival (cancer, OLT or death) was prolonged in the PSC-CD group compared to the PSC-UC group (Cox regression, p=0.04).[39] The authors postulate that this may be explained by the increased prevalence of small-duct PSC in PSC-CD patients compared to PSC-UC patients, which was also suggested by Rasmussen *et al*.[52] Furthermore, in a retrospective review of 240 PSC patients, even large duct PSC-CD patients had less liver-related morbidity and mortality compared to PSC-UC patients and PSC patients without IBD.[53]

7. The effect of IBD on recurrent PSC post-OLT

PSC recurrence (rPSC) after OLT occurs in 30% to 50% of patients, usually 10 years posttransplantation.[54] Akin to the data available regarding the relationship between IBD and PSC disease progression, the presence of concomitant IBD in PSC

patients has not been unanimously identified as a risk factor for rPSC. In a systematic review of autoimmune liver diseases after transplantation, there was no statistically significant difference in the rate of rPSC in patients with and without IBD.[55] In another retrospective analysis of 31 PSC patients who underwent OLT, 5-year survival rates, infectious complications, frequency of rejection and need for re-transplantation did not differ based on whether patients had coexisting IBD.[56] Moreover, a retrospective analysis of 105 PSC patients who underwent OLT revealed no correlation between rPSC and IBD activity.[57] On the contrary however, in another study PSC patients with UC had significantly more rPSC compared to PSC patients without UC.[58] Several publications have described that an intact colon is a strong predictor of rPSC and that colectomy potentially has a protective effect against rPSC. In a cohort of 230 PSC patients who underwent OLT, colectomy pre- and peri-OLT conferred a protective effect against rPSC in the transplanted graft.[59] Moreover, an intact colon prior to OLT was the strongest predictor of rPSC. Joshi *et al*.[60] reviewed 110 PSC patients who underwent OLT to help understand the impact of IBD on graft survival. Although the mean time to rPSC following OLT and graft survival rates were similar between the PSC group and PSC-IBD group, multivariable analysis revealed that active IBD at the time of OLT was a significant predictor of graft failure. Furthermore, on univariate analysis, colectomy pre-OLT was associated with improved graft survival. The authors speculate that decreased graft survival in the posttransplant period may be related to cases of hepatic artery thrombosis in the context of active IBD. Another retrospective study of 59 PSC patients post-OLT found that the presence or severity of IBD did not affect patient survival nor the incidence of rPSC.[41] Furthermore, on multivariable analysis, colectomy pretransplant was not associated with rPSC (hazard ratio, 0.32; 95% confidence interval [CI], 0.04 to 2.51; p=0.207). Though colectomy may be beneficial in a subset of PSC-IBD patients, concerns regarding operating on decompensated PSC patients and the potential for parastomal varices postoperatively must be considered.[61]

8. The effect of IBD on acute cellular rejection post-OLT

Despite opposing evidence on the association of IBD with rPSC, data supports that PSC-IBD patients are at risk for a greater number of acute cellular rejection (ACR) episodes post-OLT.[62,63] In a retrospective chart review of 55 PSC patients who underwent OLT, the incidence of acute rejection was higher in PSC-IBD patients compared to PSC patients (27/31 vs 10/24, p=0.0006).[64] Moreover, PSC-IBD patients who were diagnosed with IBD at a younger age were more likely to develop severe acute rejection. In spite of the increased incidence of ACR in this study, 5-year survival rates and rPSC post-OLT did not vary based on the presence of concomitant IBD.

9. Colorectal dysplasia and cancer in PSC-IBD patients

Since its initial description by Broome *et al*.,[65] plenty of studies have now confirmed the increased risk of CRN (colorectal dysplasia and colorectal cancer [CRC]) in patients with PSC-IBD (Table 2).[33,66-78] Even though there are small case series that have shown contradictory findings,[15,79-83] a large meta-analysis evaluating 13,379 patients with IBD, 1,022 (7.63%) of whom had concomitant PSC, showed that there was a 3-fold increased risk of CRN and cancer among patients with PSC-IBD compared to the IBD-only population (odds ratio [OR], 3.24; 95% CI, 2.14 to 4.90).[84] This trend persisted even after evaluating CRC risk alone (OR, 3.41; 95% CI, 2.13 to 5.48). In a subgroup analysis, PSC-UC patients were found to have a higher risk of both dysplasia (OR, 2.98; 95% CI, 1.54 to 5.76) and cancer (OR, 3.01; 95% CI, 1.44 to 6.29) compared to UC-only patients, although there was high heterogeneity among the studies. Particularly, the PSC-CD population had a nonstatistically significant higher risk of CRN and cancer (OR, 2.32, p=0.133 and OR, 2.91, p=0.388, respectively). Interestingly, in one large cohort describing the risk of cancer in PSC patients, CRN risk was only increased when IBD was also present.[85] Some have suggested that the increased risk of CRN in PSC-IBD patients could be related to the presence of long-standing underdiagnosed disease and colonic inflammation.[82] This argument has been disputed by some reports describing the same duration of IBD in the PSC and non-PSC population in patients with CRC.[86,87] However, there may be a bias since PSC patients may have a subclinical IBD phase, leading to an underestimation of the actual burden of disease.[88] Most importantly, Navaneethan *et al*.[89] suggested a higher risk in the first 2 years after diagnosis of PSC-UC, but did not find any increased risk in the subsequent years, which decreases the likelihood that a longer disease course would increase the CRN risk. There are some common features of CRN in PSC-IBD patients: extensive colon involvement,[90] more frequent CRN in the right colon (proximal to the splenic flexure);[15,33,72,73,87,91,92] and more frequent bile duct dominant stenosis (i.e., extrahepatic bile duct high-grade stenosis with obstruction).[93]

The mechanisms underlying the increased risk of CRN in PSC-IBD patients remain unknown. Different authors proposed a variety of mechanisms that may be partially responsible for this outcome (summarized in Table 3), though these are still not conclusive. In rat models, BA have been found to have a carcinogenic potential[94,95] (specifically secondary BA, like deoxycholic acid).[96] A different stool BA abundance and/or composition could potentially be involved in the right-sided CRN risk observed in PSC-IBD,[97,98] although this has never been demonstrated. Whether the specific dysbiosis that has been described in PSC-IBD could be involved in this risk remains unknown.[99-102] Other mechanisms described include inactivation of the Farnesoid X receptor pathway,[87,103,104] shown to be involved in hepatic and colonic inflammation and CRC, and

Table 2. Studies Evaluating the Risk of Colorectal Neoplasia in PSC-IBD Patients

Study	Year	Type of study	No. of patients	Outcome
Broome *et al*.[65]	1992	Prospective	72 UC patients followed to see presence of CRN	28% of patients with CRN and/or DNA aneuploidy had IBD and PSC, which was statistically significant (p=0.0004).
Broome *et al*.[69]	1995	Prospective	40 Patients with PSC-UC vs 2 groups of 40 UC-only patients	Risk of CRN in PSC-UC was 9%, 31%, and 50% after 10, 20, and 25 years of disease, compared to 2%, 5%, and 10% in UC-only patients (p<0.001).
Brentnall *et al*.[70]	1996	Prospective	20 Patients with PSC-UC vs 25 UC-only patients	Colonic neoplasia was present in 45% of PSC-UC patients, vs 16% in UC-only (p=0.002).
Leidenius *et al*.[71]	1997	Retrospective	48 Patients with PSC-UC vs 45 UC-only patients	CRN presented in 29% of PSC-UC patients, vs 9% in UC-only (p<0.05).
Marchesa *et al*.[72]	1997	Retrospective	27 Patients with PSC-UC vs 1,185 UC-only patients	Colonic neoplasia was present in 59.5% of PSC-UC patients vs 11.5% in UC-only patients (RR, 6.9; 95% CI, 3.0–16.0).
Shetty *et al*.[73]	1999	Prospective	132 Patients with PSC-UC vs 196 UC-only patients	CRN presented in 25% of PSC-UC patients, vs 5.6% in UC-only (adjusted RR, 3.15; 95% CI, 1.37–7.27; p<0.001).
Jess *et al*.[74]	2007	Retrospective	43 Patients with CRN, vs 102 control patients	PSC was associated with a higher risk of developing CRN (OR, 6.9; 95% CI, 1.2–40).
Terg *et al*.[75]	2008	Prospective	1,333 Patients with UC-39 had PSC, which were matched to two control patients	CRC presented in 18% of PSC-UC patients, vs 2.6% in matched UC-only patients (p=0.006). Risk of CRC in PSC-UC was 11% and 18% after 10 and 20 years vs 2% and 7% in UC-only, respectively (p=0.002).
Sokol *et al*.[33]	2008	Prospective	75 Patients with PSC-IBD vs 152 IBD-only patients	25 Years cumulative risk of CRN was 23.4% in PSC-IBD vs 0% in IBD-only (p=0.002). PSC was a risk factor for CRC (OR, 10.8; 95% CI, 3.7–31.3).
Lindstrom *et al*.[76]	2011	Prospective	28 Patients with PSC-CD vs 46 CD-only patients	CRN presented in 32% of PSC-CD patients, vs 7% in CD-only (OR, 6.78; 95% CI, 1.65–27.9; p=0.016).
Ananthakrishnan *et al*.[77]	2014	Retrospective	224 Patients with PSC-IBD, from a pool of 5,506 CD and 5,522 UC patients	PSC-IBD had a higher risk of CRC (OR, 5.00; 95% CI, 2.80–8.95) and digestive tract cancer (OR, 10.4; 95% CI, 6.86–15.76), compared to IBD-only patients.
Navaneethan *et al*.[78]	2016	Retrospective	223 Patients with PSC-UC vs 50 with PSC-CD	PSC-UC patients had higher risk for colonic neoplasia compared to PSC-CD (35.9% vs 18%, p=0.009).

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CRN, colorectal neoplasia; RR, relative risk; CI, confidence interval; OR, odds ratio; CD, Crohn's disease.

Table 3. Proposed Mechanisms for the Increased Risk of Colorectal Neoplasia in PSC-IBD Patients

Mechanism	Explanation
Genetic	Polymorphisms present in TNFα promoter and specific genome associations in proximity to HLA complex on chromosome 6p21 have been associated with a higher likelihood of developing CRN.
Bile acid	Cholestasis favors decreased intestinal BA reabsorption. Microbiota convert primary BA to secondary BA, which have a carcinogenic potential.
FXR pathway	FX secretion by the intestine is induced by the presence of BA. Normally, FX leads to a decrease in the production of BA by the liver.
Microbiome	Gut bacteria are presumed to act on altered BA composition resulting in proinflammatory and procarcinogenic compounds.

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; HLA, human leukocyte antigen; CRN, colorectal neoplasia; BA, bile acid; FXR, farnesoid X receptor; FX, farnesoid X.

polymorphisms in two genes in the chromosome 6p21. A more comprehensive understanding of the PSC pathogenesis and the involved BA dysmetabolism and microbiota dysbiosis will probably help to clarify the mechanisms involved in the increased CRN risk in these patients.

One would hypothesize that once indefinite or low-grade dysplasia (LGD) is diagnosed in PSC-IBD, the rate of progression to high-grade dysplasia or CRC would be faster than in IBD patients. However, while some studies have described the rate of progression of indefinite and LGD in IBD-only patients, the rate of progression of CRN in patients with PSC-IBD has not been thoroughly studied. In a small study with 10 patients, one-third of the patients progressed from LGD to advanced neoplasia over a mean follow-up of 13±11 months, suggesting a faster rate of progression as compared to what has been described in IBD alone.[105]

Since many patients with PSC require OLT,[106] some uncertainty exists regarding the effect of the strong immunosuppressive agents in the post-OLT setting, leading to an increased risk for CRN versus the "protective" effect of curing the PSC on the risk of CRN. Some of the initial studies[107,108] showed that there was no difference in the rate of CRN in the post-OLT PSC-IBD group compared to post-OLT non-IBD/PSC and nontransplanted PSC-IBD patients. More recent studies have suggested that there may be even a 4-fold greater risk of CRN, though there was no evidence of any relevant impact on mortality.[109,110] Particularly, one study suggested that patients who developed LGD after OLT had a slower rate of progression and were less likely to have progressive neoplasia or persistent LGD.[111]

Another subset of the PSC-IBD population who are at risk for neoplasia are the patients who have undergone an IPAA, given that their increased incidence of pouchitis theoretically leads to severe mucosal atrophy and subsequent pouch malignancy.[112] Although a small study showed an increased risk of ileal pouch dysplasia in PSC-IBD compared to non-IBD and non-PSC populations separately,[113] a larger study that included 65 patients suggested a low risk of 5.6% in 5-year for pouch or cuff dysplasia (95% CI, 1.8% to 16.1%).[114] Particularly, CRC has been documented but is extremely uncommon after IPAA.[115] There are no specific surveillance guidelines for post-IPAA PSC-IBD patients, so most experts prefer annual pouchoscopies as standard care for PSC patients, even though the risk seems to be low.

Given that the risks of CRN have been widely described in the PSC-IBD population, the different gastroenterology societies have commented on recommendations for surveillance in this group. Current recommendations support the use of annual colonoscopy and biopsies in PSC-IBD patients from the time of PSC diagnosis, without taking into account the duration of IBD since it is often not known.[116,117] No specific recommendations on the management and follow-up of indefinite or LGD exist for this high-risk population that may be more prone to be referred for colectomy, given the elevated risk of CRC. Hence, further studies are needed to better determine the outcomes regarding low-grade and indefinite dysplasia in PSC-IBD patients.

UDCA[118] has been in the past considered an option in the prevention of CRN in PSC-IBD patients. However, studies have shown mixed results: some of them with decreased risk of CRN,[119,120] others not showing any effect in the incidence of neoplasia,[89,121,122] and others even showing an increased risk with high-dose UDCA, usually in the first 6 years after the medication was started.[123] A meta-analysis in 2013, evaluating eight studies with 763 PSC-IBD patients, concluded that there is a preventive effect for the development of advanced CRN when taking UDCA (OR, 0.35; 95% CI, 0.17 to 0.73), with a more pronounced effect with the 8 to 15 mg/kg/day dose (OR, 0.19; 95% CI, 0.08 to 0.49).[124] Therefore, while there might be a protective effect, more studies are needed to draw more definitive conclusions.

10. Biliary cancer risk in PSC-IBD patients

In a recent large retrospective review of 399 PSC-IBD patients from the Mayo Clinic, a prolonged duration of IBD was associated with an increased risk of cholangiocarcinoma (CCA) in PSC patients.[125] This increased risk equated to a 33% increased risk per 10 years of IBD and the risk was not modified by colectomy. Furthermore, in the subset of PSC-IBD patients requiring colectomy, patients who underwent surgery due to colonic neoplasia or dysplasia as opposed to refractory disease were also at a significantly higher risk of CCA. From an earlier published study conducted at Mayo Clinic, although IBD was not associated with CCA risk, proctocolectomy was a significant risk factor on univariate analysis for the development of CCA in PSC patients (relative risk, 4.43).[126] It is unclear if the observed elevated cancer risk may be secondary to the effect of immunosuppression or the severity of intestinal inflammation.

The increased predisposition to malignant transformation may not only apply to the biliary system in PSC-IBD patients. From a population-based study in New Zealand, 14 of 60 PSC-IBD patients developed a malignant complication including CRC, hepatocellular carcinoma or CCA whereas none of the 19 PSC patients without IBD did.[51] Nevertheless, in another study of 66 PSC patients, the prevalence of malignant complications was not dependent on the presence or absence of IBD,[46] nor did it play a role in a natural history study of 305 Swedish PSC patients[49] or a long-term single-center study of 200 PSC patients.[127]

CONCLUSIONS

IBD affects about 70% of patients with PSC. Although there is likely an underlying shared predisposition for PSC and IBD, the pathogenesis of these interrelated conditions is still unknown. These diseases are likely to be influenced by genetic predisposition, immune-mediated processes and altered gut microbiota.

Clinically, PSC-IBD patients demonstrate a right-to-left gradient of colonic inflammation as well as an increased incidence of extensive colitis, rectal sparing and backwash ileitis. Despite the higher prevalence of pancolitis, the intestinal inflammation is usually quiescent leading to mild symptoms, reduced use of steroids and decreased rates of hospitalization. Nevertheless, post-IPAA, the rates of pouchitis in PSC-UC patients are higher compared to non-PSC UC patients. While PSC is associated with a distinct IBD phenotype, the effect of IBD on the natural history and disease behavior of PSC, including recurrent PSC post-OLT, is less well defined. Overall, the PSC-IBD population has an increased risk of developing CRN and CRC compared to the IBD-only population. Moreover, IBD may also be also associated with an increased risk of CCA in PSC patients.

In summary, PSC-IBD is a puzzling disease with a very special phenotype (Fig. 2); a better understanding of the mechanisms underlying the cross talk between the liver and the gut is needed and could lead to the development of new strategies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016;10:239-254.
2. Smith MP, Loe RH. Sclerosing cholangitis; review of recent case reports and associated diseases and four new cases. Am J Surg 1965;110:239-246.
3. Rossi RE, Conte D, Massironi S. Primary sclerosing cholangitis associated with inflammatory bowel disease: an update. Eur J Gastroenterol Hepatol 2016;28:123-131.
4. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol 1998;33:99-103.
5. Molodecky NA, Kareemi H, Parab R, et al. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology 2011;53:1590-1599.
6. de Vries AB, Janse M, Blokzijl H, Weersma RK. Distinctive inflammatory bowel disease phenotype in primary sclerosing cholangitis. World J Gastroenterol 2015;21:1956-1971.
7. Tanaka A, Takamori Y, Toda G, Ohnishi S, Takikawa H. Outcome and prognostic factors of 391 Japanese patients with primary sclerosing cholangitis. Liver Int 2008;28:983-989.
8. Shorbagi A, Bayraktar Y. Primary sclerosing cholangitis: what is the difference between east and west? World J Gastroenterol 2008;14:3974-3981.
9. Sano H, Nakazawa T, Ando T, et al. Clinical characteristics of inflammatory bowel disease associated with primary sclerosing cholangitis. J Hepatobiliary Pancreat Sci 2011;18:154-161.
10. Schaeffer DF, Win LL, Hafezi-Bakhtiari S, Cino M, Hirschfield GM, El-Zimaity H. The phenotypic expression of inflammatory bowel disease in patients with primary sclerosing cholangitis differs in the distribution of colitis. Dig Dis Sci 2013;58:2608-2614.
11. Nakazawa T, Naitoh I, Hayashi K, et al. Inflammatory bowel disease of primary sclerosing cholangitis: a distinct entity? World J Gastroenterol 2014;20:3245-3254.
12. Jorgensen KK, Grzyb K, Lundin KE, et al. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients. Inflamm Bowel Dis 2012;18:536-45.
13. Sinakos E, Samuel S, Enders F, Loftus EV Jr, Sandborn WJ, Lindor KD. Inflammatory bowel disease in primary sclerosing cholangitis: a robust yet changing relationship. Inflamm Bowel Dis 2013;19:1004-1009.
14. Rojas-Feria M, Castro M, Suarez E, Ampuero J, Romero-Gomez M. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. World J Gastroenterol 2013;19:7327-7340.
15. Loftus EV Jr, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut 2005;54:91-96.
16. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491:119-124.
17. Huang C, Haritunians T, Okou DT, et al. Characterization of genetic loci that affect susceptibility to inflammatory bowel diseases in African Americans. Gastroenterology 2015;149:1575-1586.
18. Henriksen EK, Melum E, Karlsen TH. Update on primary sclerosing cholangitis genetics. Curr Opin Gastroenterol 2014;30:310-319.
19. Liu JZ, Hov JR, Folseraas T, et al. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. Nat Genet 2013;45:670-675.
20. Tsaitas C, Semertzidou A, Sinakos E. Update on inflammatory bowel disease in patients with primary sclerosing cholangitis. World J Hepatol 2014;6:178-187.
21. Grant AJ, Lalor PF, Salmi M, Jalkanen S, Adams DH. Homing of mucosal lymphocytes to the liver in the pathogenesis of hepatic complications of inflammatory bowel disease. Lancet 2002;359:150-157.
22. Adams DH, Eksteen B. Aberrant homing of mucosal T cells and

extra-intestinal manifestations of inflammatory bowel disease. Nat Rev Immunol 2006;6:244-251.
23. Eksteen B, Grant AJ, Miles A, et al. Hepatic endothelial CCL25 mediates the recruitment of CCR9+ gut-homing lymphocytes to the liver in primary sclerosing cholangitis. J Exp Med 2004;200:1511-1517.
24. Cesaro C, Tiso A, Del Prete A, et al. Gut microbiota and probiotics in chronic liver diseases. Dig Liver Dis 2011;43:431-438.
25. Tabibian JH, Varghese C, LaRusso NF, O'Hara SP. The enteric microbiome in hepatobiliary health and disease. Liver Int 2016;36:480-487.
26. Torres J, Pineton de Chambrun G, Itzkowitz S, Sachar DB, Colombel JF. Review article: colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease. Aliment Pharmacol Ther 2011;34:497-508.
27. Duboc H, Rajca S, Rainteau D, et al. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. Gut 2013;62:531-539.
28. Quraishi MN, Sergeant M, Kay G, et al. The gut-adherent microbiota of PSC-IBD is distinct to that of IBD. Gut 2017;66:386-388.
29. Kummen M, Holm K, Anmarkrud JA, et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. Gut 2017;66:611-619.
30. Tabibian JH, O'Hara SP, Trussoni CE, et al. Absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis. Hepatology 2016;63:185-196.
31. Joo M, Abreu-e-Lima P, Farraye F, et al. Pathologic features of ulcerative colitis in patients with primary sclerosing cholangitis: a case-control study. Am J Surg Pathol 2009;33:854-862.
32. Olsson R, Danielsson A, Jarnerot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology 1991;100:1319-1323.
33. Sokol H, Cosnes J, Chazouilleres O, et al. Disease activity and cancer risk in inflammatory bowel disease associated with primary sclerosing cholangitis. World J Gastroenterol 2008;14:3497-3503.
34. Ye BD, Yang SK, Boo SJ, et al. Clinical characteristics of ulcerative colitis associated with primary sclerosing cholangitis in Korea. Inflamm Bowel Dis 2011;17:1901-1906.
35. Marelli L, Xirouchakis E, Kalambokis G, Cholongitas E, Hamilton MI, Burroughs AK. Does the severity of primary sclerosing cholangitis influence the clinical course of associated ulcerative colitis? Gut 2011;60:1224-1228.
36. O'Toole A, Alakkari A, Keegan D, Doherty G, Mulcahy H, O'Donoghue D. Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. Clin Gastroenterol Hepatol 2012;10:439-441.
37. Boonstra K, van Erpecum KJ, van Nieuwkerk KM, et al. Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. Inflamm Bowel Dis 2012;18:2270-2276.
38. Gelley F, Miheller P, Peter A, Telkes G, Nemes B. Activity of ulcerative colitis before and after liver transplantation in primary sclerosing cholangitis: the Hungarian experience. Transplant Proc 2012;44:2164-2165.
39. Halliday JS, Djordjevic J, Lust M, et al. A unique clinical phenotype of primary sclerosing cholangitis associated with Crohn's disease. J Crohns Colitis 2012;6:174-181.
40. Singh S, Talwalkar JA. Primary sclerosing cholangitis: diagnosis, prognosis, and management. Clin Gastroenterol Hepatol 2013;11:898-907.
41. Moncrief KJ, Savu A, Ma MM, Bain VG, Wong WW, Tandon P. The natural history of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation: a single-centre experience. Can J Gastroenterol 2010;24:40-46.
42. Verdonk RC, Dijkstra G, Haagsma EB, et al. Inflammatory bowel disease after liver transplantation: risk factors for recurrence and de novo disease. Am J Transplant 2006;6:1422-1429.
43. Haagsma EB, Van Den Berg AP, Kleibeuker JH, Slooff MJ, Dijkstra G. Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens. Aliment Pharmacol Ther 2003;18:33-44.
44. Verdonk RC, Haagsma EB, Jonker MR, et al. Effects of different immunosuppressive regimens on regulatory T-cells in noninflamed colon of liver transplant recipients. Inflamm Bowel Dis 2007;13:703-709.
45. Mathis KL, Benavente-Chenhalls LA, Dozois EJ, Wolff BG, Larson DW. Short- and long-term surgical outcomes in patients undergoing proctocolectomy with ileal pouch-anal anastomosis in the setting of primary sclerosing cholangitis. Dis Colon Rectum 2011;54:787-792.
46. Rabinovitz M, Gavaler JS, Schade RR, Dindzans VJ, Chien MC, Van Thiel DH. Does primary sclerosing cholangitis occurring in association with inflammatory bowel disease differ from that occurring in the absence of inflammatory bowel disease? A study of sixty-six subjects. Hepatology 1990;11:7-11.
47. Navaneethan U, Venkatesh PG, Lashner BA, Shen B, Kiran RP. The impact of ulcerative colitis on the long-term outcome of patients with primary sclerosing cholangitis. Aliment Pharmacol Ther 2012;35:1045-1053.
48. Yanai H, Matalon S, Rosenblatt A, et al. Prognosis of primary sclerosing cholangitis in israel is independent of coexisting inflammatory bowel Disease. J Crohns Colitis 2015;9:177-184.
49. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996;38:610-615.
50. Ludwig J, Barham SS, LaRusso NF, Elveback LR, Wiesner RH, McCall JT. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis and chronic ulcerative colitis. Hepatology 1981;1:632-640.
51. Ngu JH, Gearry RB, Wright AJ, Stedman CA. Inflammatory bowel disease is associated with poor outcomes of patients with primary

sclerosing cholangitis. Clin Gastroenterol Hepatol 2011;9:1092-1097.
52. Rasmussen HH, Fallingborg JF, Mortensen PB, Vyberg M, Tage-Jensen U, Rasmussen SN. Hepatobiliary dysfunction and primary sclerosing cholangitis in patients with Crohn's disease. Scand J Gastroenterol 1997;32:604-610.
53. Fevery J, Van Steenbergen W, Van Pelt J, et al. Patients with large-duct primary sclerosing cholangitis and Crohn's disease have a better outcome than those with ulcerative colitis, or without IBD. Aliment Pharmacol Ther 2016;43:612-620.
54. Singh S, Loftus EV Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Am J Gastroenterol 2013;108:1417-1425.
55. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. Liver Transpl 2006;12:1813-1824.
56. van de Vrie W, de Man RA, van Buuren HR, Schouten WR, Tilanus HW, Metselaar HJ. Inflammatory bowel disease and liver transplantation for primary sclerosing cholangitis. Eur J Gastroenterol Hepatol 2003;15:657-663.
57. Mosli M, Croome K, Qumosani K, et al. The effect of liver transplantation for primary sclerosing cholangitis on disease activity in patients with inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2013;9:434-441.
58. Cholongitas E, Shusang V, Papatheodoridis GV, et al. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl 2008;14:138-143.
59. Alabraba E, Nightingale P, Gunson B, et al. A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. Liver Transpl 2009;15:330-340.
60. Joshi D, Bjarnason I, Belgaumkar A, et al. The impact of inflammatory bowel disease post-liver transplantation for primary sclerosing cholangitis. Liver Int 2013;33:53-61.
61. Fucini C, Wolff BG, Dozois RR. Bleeding from peristomal varices: perspectives on prevention and treatment. Dis Colon Rectum 1991;34:1073-1078.
62. Graziadei IW, Wiesner RH, Marotta PJ, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. Hepatology 1999;30:1121-1127.
63. Narumi S, Roberts JP, Emond JC, Lake J, Ascher NL. Liver transplantation for sclerosing cholangitis. Hepatology 1995;22:451-457.
64. Miki C, Harrison JD, Gunson BK, Buckels JA, McMaster P, Mayer AD. Inflammatory bowel disease in primary sclerosing cholangitis: an analysis of patients undergoing liver transplantation. Br J Surg 1995;82:1114-1147.
65. Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis: a risk factor for the development of dysplasia and DNA aneuploidy? Gastroenterology 1992;102:1877-1880.
66. D'Haens GR, Lashner BA, Hanauer SB. Pericholangitis and sclerosing cholangitis are risk factors for dysplasia and cancer in ulcerative colitis. Am J Gastroenterol 1993;88:1174-1178.
67. Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. Gut 1997;41:522-525.
68. Kaplan GG, Heitman SJ, Hilsden RJ, et al. Population-based analysis of practices and costs of surveillance for colonic dysplasia in patients with primary sclerosing cholangitis and colitis. Inflamm Bowel Dis 2007;13:1401-1407.
69. Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. Hepatology 1995;22:1404-1408.
70. Brentnall TA, Haggitt RC, Rabinovitch PS, et al. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1996;110:331-338.
71. Leidenius MH, Farkkila MA, Karkkainen P, Taskinen EI, Kellokumpu IH, Hockerstedt KA. Colorectal dysplasia and carcinoma in patients with ulcerative colitis and primary sclerosing cholangitis. Scand J Gastroenterol 1997;32:706-711.
72. Marchesa P, Lashner BA, Lavery IC, et al. The risk of cancer and dysplasia among ulcerative colitis patients with primary sclerosing cholangitis. Am J Gastroenterol 1997;92:1285-1288.
73. Shetty K, Rybicki L, Brzezinski A, Carey WD, Lashner BA. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. Am J Gastroenterol 1999;94:1643-1649.
74. Jess T, Loftus EV Jr, Velayos FS, et al. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. Am J Gastroenterol 2007;102:829-836.
75. Terg R, Sambuelli A, Coronel E, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis and the risk of developing malignancies: a large prospective study. Acta Gastroenterol Latinoam 2008;38:26-33.
76. Lindstrom L, Lapidus A, Ost A, Bergquist A. Increased risk of colorectal cancer and dysplasia in patients with Crohn's colitis and primary sclerosing cholangitis. Dis Colon Rectum 2011;54:1392-1397.
77. Ananthakrishnan AN, Cagan A, Gainer VS, et al. Mortality and extraintestinal cancers in patients with primary sclerosing cholangitis and inflammatory bowel disease. J Crohns Colitis 2014;8:956-963.
78. Navaneethan U, Venkatesh PG, Jegadeesan R, et al. Comparison of outcomes for patients with primary sclerosing cholangitis associated with ulcerative colitis and Crohn's disease. Gastroenterol Rep (Oxf) 2016;4:43-49.
79. Choi PM, Nugent FW, Rossi RL. Relationship between colorectal neoplasia and primary sclerosing cholangitis in ulcerative colitis. Gastroenterology 1992;103:1707-1709.
80. Gurbuz AK, Giardiello FM, Bayless TM. Colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Dis Colon Rectum 1995;38:37-41.

81. Loftus EV Jr, Sandborn WJ, Tremaine WJ, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis. Gastroenterology 1996;110:432-440.
82. Nuako KW, Ahlquist DA, Sandborn WJ, Mahoney DW, Siems DM, Zinsmeister AR. Primary sclerosing cholangitis and colorectal carcinoma in patients with chronic ulcerative colitis: a case-control study. Cancer 1998;82:822-826.
83. Aitola P, Mattila J, Matikainen M. Liver involvement in patients operated for ulcerative colitis, with special reference to the association of cholangitis with colorectal dysplasia and carcinoma. Int J Colorectal Dis 2000;15:167-171.
84. Zheng HH, Jiang XL. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies. Eur J Gastroenterol Hepatol 2016;28:383-390.
85. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol 2002;36:321-327.
86. Brackmann S, Andersen SN, Aamodt G, et al. Relationship between clinical parameters and the colitis-colorectal cancer interval in a cohort of patients with colorectal cancer in inflammatory bowel disease. Scand J Gastroenterol 2009;44:46-55.
87. Lindberg BU, Broome U, Persson B. Proximal colorectal dysplasia or cancer in ulcerative colitis. The impact of primary sclerosing cholangitis and sulfasalazine: results from a 20-year surveillance study. Dis Colon Rectum 2001;44:77-85.
88. Broome U, Lofberg R, Lundqvist K, Veress B. Subclinical time span of inflammatory bowel disease in patients with primary sclerosing cholangitis. Dis Colon Rectum 1995;38:1301-1305.
89. Navaneethan U, Kochhar G, Venkatesh PG, et al. Duration and severity of primary sclerosing cholangitis is not associated with risk of neoplastic changes in the colon in patients with ulcerative colitis. Gastrointest Endosc 2012;75:1045-1054.
90. Singh S, Edakkanambeth Varayil J, Loftus EV Jr, Talwalkar JA. Incidence of colorectal cancer after liver transplantation for primary sclerosing cholangitis: a systematic review and meta-analysis. Liver Transpl 2013;19:1361-1369.
91. Claessen MM, Lutgens MW, van Buuren HR, et al. More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis. Inflamm Bowel Dis 2009;15:1331-1336.
92. Thackeray EW, Charatcharoenwitthaya P, Elfaki D, Sinakos E, Lindor KD. Colon neoplasms develop early in the course of inflammatory bowel disease and primary sclerosing cholangitis. Clin Gastroenterol Hepatol 2011;9:52-56.
93. Rudolph G, Gotthardt D, Kloeters-Plachky P, Rost D, Kulaksiz H, Stiehl A. In PSC with dominant bile duct stenosis, IBD is associated with an increase of carcinomas and reduced survival. J Hepatol 2010;53:313-317.
94. Hill MJ. Bile flow and colon cancer. Mutat Res 1990;238:313-320.
95. Bernstein C, Holubec H, Bhattacharyya AK, et al. Carcinogenicity of deoxycholate, a secondary bile acid. Arch Toxicol 2011;85:863-871.
96. Kanamoto R, Azuma N, Suda H, Saeki T, Tsuchihashi Y, Iwami K. Elimination of Na+-dependent bile acid transporter from small intestine by ileum resection increases [correction of increase] colonic tumorigenesis in the rat fed deoxycholic acid. Cancer Lett 1999;145:115-120.
97. Hruz P, Zimmermann C, Gutmann H, et al. Adaptive regulation of the ileal apical sodium dependent bile acid transporter (ASBT) in patients with obstructive cholestasis. Gut 2006;55:395-402.
98. Sauer P, Stiehl A, Fitscher BA, et al. Downregulation of ileal bile acid absorption in bile-duct-ligated rats. J Hepatol 2000;33:2-8.
99. Tlaskalova-Hogenova H, Stepankova R, Kozakova H, et al. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: contribution of germ-free and gnotobiotic animal models of human diseases. Cell Mol Immunol 2011;8:110-120.
100. Sellon RK, Tonkonogy S, Schultz M, et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. Infect Immun 1998;66:5224-5231.
101. Lai KK, Horvath B, Xie H, et al. Risk for colorectal neoplasia in patients with inflammatory bowel disease and mucosa indefinite for dysplasia. Inflamm Bowel Dis 2015;21:378-384.
102. Begley M, Gahan CG, Hill C. The interaction between bacteria and bile. FEMS Microbiol Rev 2005;29:625-651.
103. Modica S, Murzilli S, Salvatore L, Schmidt DR, Moschetta A. Nuclear bile acid receptor FXR protects against intestinal tumorigenesis. Cancer Res 2008;68:9589-9594.
104. Vavassori P, Mencarelli A, Renga B, Distrutti E, Fiorucci S. The bile acid receptor FXR is a modulator of intestinal innate immunity. J Immunol 2009;183:6251-6261.
105. Venkatesh PG, Jegadeesan R, Gutierrez NG, Sanaka MR, Navaneethan U. Natural history of low grade dysplasia in patients with primary sclerosing cholangitis and ulcerative colitis. J Crohns Colitis 2013;7:968-973.
106. Wiesner RH. Liver transplantation for primary sclerosing cholangitis: timing, outcome, impact of inflammatory bowel disease and recurrence of disease. Best Pract Res Clin Gastroenterol 2001;15:667-680.
107. Dvorchik I, Subotin M, Demetris AJ, et al. Effect of liver transplantation on inflammatory bowel disease in patients with primary sclerosing cholangitis. Hepatology 2002;35:380-384.
108. Hanouneh IA, Macaron C, Lopez R, Zein NN, Lashner BA. Risk of colonic neoplasia after liver transplantation for primary sclerosing cholangitis. Inflamm Bowel Dis 2012;18:269-274.
109. Loftus EV Jr, Aguilar HI, Sandborn WJ, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. Hepatology 1998;27:685-690.
110. Vera A, Gunson BK, Ussatoff V, et al. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation 2003;75:1983-

1988.

111. Eaton JE, Smyrk TC, Imam M, et al. The fate of indefinite and low-grade dysplasia in ulcerative colitis and primary sclerosing cholangitis colitis before and after liver transplantation. Aliment Pharmacol Ther 2013;38:977-987.
112. Gullberg K, Stahlberg D, Liljeqvist L, et al. Neoplastic transformation of the pelvic pouch mucosa in patients with ulcerative colitis. Gastroenterology 1997;112:1487-1492.
113. Stahlberg D, Veress B, Tribukait B, Broome U. Atrophy and neoplastic transformation of the ileal pouch mucosa in patients with ulcerative colitis and primary sclerosing cholangitis: a case control study. Dis Colon Rectum 2003;46:770-778.
114. Imam MH, Eaton JE, Puckett JS, et al. Neoplasia in the ileoanal pouch following colectomy in patients with ulcerative colitis and primary sclerosing cholangitis. J Crohns Colitis 2014;8:1294-1299.
115. Rahman M, Desmond P, Mortensen N, Chapman RW. The clinical impact of primary sclerosing cholangitis in patients with an ileal pouch-anal anastomosis for ulcerative colitis. Int J Colorectal Dis 2011;26:553-559.
116. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010;138:738-745.
117. Biancone L, Michetti P, Travis S, et al. European evidence-based consensus on the management of ulcerative colitis: special situations. J Crohns Colitis 2008;2:63-92.
118. Batta AK, Salen G, Holubec H, Brasitus TA, Alberts D, Earnest DL. Enrichment of the more hydrophilic bile acid ursodeoxycholic acid in the fecal water-soluble fraction after feeding to rats with colon polyps. Cancer Res 1998;58:1684-1687.
119. Tung BY, Emond MJ, Haggitt RC, et al. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Ann Intern Med 2001;134:89-95.
120. Pardi DS, Loftus EV Jr, Kremers WK, Keach J, Lindor KD. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. Gastroenterology 2003;124:889-893.
121. Wolf JM, Rybicki LA, Lashner BA. The impact of ursodeoxycholic acid on cancer, dysplasia and mortality in ulcerative colitis patients with primary sclerosing cholangitis. Aliment Pharmacol Ther 2005;22:783-788.
122. Lindstrom L, Boberg KM, Wikman O, et al. High dose ursodeoxycholic acid in primary sclerosing cholangitis does not prevent colorectal neoplasia. Aliment Pharmacol Ther 2012;35:451-457.
123. Rudolph G, Gotthardt DN, Kloeters-Plachky P, Kulaksiz H, Schirmacher P, Stiehl A. In PSC with colitis treated with UDCA, most colonic carcinomas develop in the first years after the start of treatment. Dig Dis Sci 2011;56:3624-3630.
124. Singh S, Khanna S, Pardi DS, Loftus EV Jr, Talwalkar JA. Effect of ursodeoxycholic acid use on the risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis 2013;19:1631-1638.
125. Gulamhusein AF, Eaton JE, Tabibian JH, Atkinson EJ, Juran BD, Lazaridis KN. Duration of inflammatory bowel disease is associated with increased risk of cholangiocarcinoma in patients with primary sclerosing cholangitis and IBD. Am J Gastroenterol 2016;111:705-711.
126. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol 2004;99:523-526.
127. Fevery J, Henckaerts L, Van Oirbeek R, et al. Malignancies and mortality in 200 patients with primary sclerosering cholangitis: a long-term single-centre study. Liver Int 2012;32:214-222.