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All you need to know about the overlap between primary sclerosing cholangitis and inflammatory bowel disease

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Abstract

Primary sclerosing cholangitis (PSC) is a progressive auto-inflammatory condition of the biliary ducts clinically characterized by painless cholestasis and jaundice. Histologically, the typical findings in PSC are periductal fibrosis with inflammation, bile duct proliferation, and ductopenia. These hallmarks eventually develop into end-stage liver disease requiring liver transplantation (LT), although the latency between diagnosis and LT is variable among patients. PSC is the leading indication for LT among patients with autoimmune liver disease. The interplay of PSC and inflammatory bowel disease (IBD) is intricate and poorly understood, as exemplified by the ongoing debate as to whether these are 2 distinct diseases or a complex 2-sided manifestation of the same disease spectrum. A true pathophysiological pathway has not been pinpointed, which explains the current lack of disease-specific therapies approved for this entity. This review summarizes our current knowledge about the epidemiology, pathophysiology, clinical presentation and management of PSC. We will also elucidate the relationship between PSC and IBD, specifically regarding the LT and pouchitis subpopulations.

Keywords Primary sclerosing cholangitis, liver transplantation, inflammatory bowel disease, ulcerative colitis, practice management

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Introduction

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease that is commonly encountered as an extra-intestinal manifestation (EIM) of inflammatory bowel disease (IBD), and more specifically ulcerative colitis (UC). Unlike many EIMs, PSC charts its clinical course irrespectively of the underlying bowel inflammation. PSC can also occur independently of IBD, in up to 20% of all patients with PSC [1-6]. Interestingly, the diagnosis of PSC may precede or result in the diagnosis of a more indolent form of IBD, since all patients diagnosed with PSC need to get a colonoscopy at the time of their PSC diagnosis. Although strong evidence suggests an increased risk, and usually an earlier presentation, of colorectal cancer (CRC) in patients with concomitant PSC and IBD, controversy still exists as to whether or not concomitant PSC implies an increased risk of a complicated IBD course, such as resistance to IBD-related medical therapy, or medically refractory pouchitis in patients with ileal pouches. For this reason, it is imperative to identify the presence of concomitant PSC in patients with IBD [7,8]. Some experts consider the "PSC-IBD" entity as phenotypically different from either PSC or IBD alone.

Despite the expansion of the therapeutic armamentarium for IBD, no therapy is currently approved for the treatment of PSC, and liver transplantation (LT) remains the sole therapeutic option. Unfortunately, it is not uncommon for the PSC to recur in the transplanted liver [9]. In addition, the literature has been inconclusive regarding the impact of IBD on PSC outcomes, namely progression to cirrhosis and post-LT PSC recurrence.

The scientific community is researching the pathophysiological links between PSC and IBD, considering environmental factors, microbiome, bile acid metabolites and transcriptome signatures, in hopes of identifying therapeutic targets. Additionally, attempts at identifying individuals at high risk of developing these phenotypes may aid in the

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early detection and treatment of these patients. This review sheds light on PSC, its relationship with IBD, and the clinical considerations for managing patients across the spectrum of both entities.

Pathogenesis

No single unifying mechanism can currently explain the pathogenesis of PSC; this, in turn, contributes to our inability to clearly understand whether PSC and IBD are entirely separate entities with some common progenitor event, or are pathologically linked. There are conflicting data on whether bile acid signaling, aberrant lymphocyte trafficking, leaky gut, and dysbiosis are a result or a cause of PSC [10].

Colonic dysbiosis is one of several theories linking the gut to hepatic inflammation in patients with PSC, mainly through the trafficking of toxins and immunostimulatory chemokines from the colon to the liver via the portal vein, leading to bile duct injury. Studies that support this theory identify *Veillonella* or *Klebsiella pneumoniae* pathogen-associated molecular patterns (PAMPs), or acute phase protein lipopolysaccharide binding proteins, among others, that are likely to cross a damaged colonic epithelial barrier in patients with active IBD [11,12]. These microbiota signatures are unique to PSC-IBD, when compared to both patients with only IBD and healthy controls [13,14]. Impaired mucosal lining secondary to inflammation in IBD can facilitate the translocation of these inflammatory signals in what is called a "leaky gut phenomenon". In addition to the pathobiont pathway, proximal colonic inflammation also affects the bile acid reabsorption cycle and metabolism of primary bile acids, which in turn disturbs the bile acid feedback hepatic signaling and damages the biliary system through toxic bile acid levels [15]. Other theories come from the discovery of inappropriate T cells with gut-specific homing signals (i.e., MAdCAM-1 and CCL20) in the portal systems after they interact with gut dendritic cells or M cells [16]. These Th17-positive T lymphocytes could burden the liver with inflammatory damage [17]. Nevertheless, these associations are not linear, as some studies show that severe colonic inflammation may in fact decrease cholestatic injury, which is reflected clinically by inverse associations between progressive PSC and colitis severity [18,19]. It is worth noting that these theories are not mutually exclusive, and the sequence of cause and effect is not so clear. For instance, decreasing gut permeability through control of inflammation and dysbiosis may in turn improve bile acid signaling or correct T lymphocyte differentiation. Some research indicates that bile acids modulate colonic MAdCAM-1 expression, and not the reverse [20]. Dysbiosis may aid the depletion of butyric acid, an important source of colonocyte nutrition and an anti-inflammatory signal, which in turn could affect mucosal permeability and immunomodulatory functions [21]. Studies on fecal transplants from humans with PSC to healthy mice that develop hepatobiliary injury further heighten this theory [11]. On the other hand, bile acids have both hepatobiliary as well as innate immunity effects [22]. If this holds true, a single treatment strategy, such as antimicrobials, may affect multiple downstream pathways simultaneously.

Genetics and PSC

PSC is associated with genetic foci involved in immune-mediated processes, such as T-lymphocyte proliferation, interferon-γ and interleukin (IL)-2 signaling, which are shared with IBD as well as other autoimmune disorders [23,24]. However, genome-wide association-based models of co-occurrence with IBD fall very short from the actual incidence of PSC occurring with IBD (1.6% projected vs. 70% real comorbid rate) [25], and a genetic linkage theory has not been proven for PSC and IBD [23]. In other words, genetics only account for less than 10% of PSC susceptibility, with limited overlap with IBD [24]. Nevertheless, some signature differences exist between patients with PSC-IBD compared to those with UC alone. Most notably, patients with PSC and UC exhibit more interferon-γ secreting T cells and innate lymphoid cells, as well as increased colonic levels of C-X-C motif chemokine receptor 3-positive CD8+ T cells, but fewer CD25-positive CD4+ T cells. However, no distinct patterns have been found in DNA methylation, adhesion molecule expression or chemokine activation [17,26,27].

Epidemiology

PSC occurs at low rates of 0.1-32 per 100,000, with higher prevalences in Northern European and North American countries, and the lowest in Asia, although some data show the highest prevalence in South America [3,28-33]. Some contemporary increases in the diagnosis rates of PSC (and PSC-IBD) may be partly due to increased awareness or the establishment of specific ICD diagnosis codes for PSC. The pattern of PSC incidence globally does follow that of IBD, and it would be interesting to see if the rise in PSC diagnosis mimics that of IBD, especially in the East, where it is postulated to be due to a "westernization" of the global diet. The incidence of PSC is 10-fold higher in first-degree relatives compared to the general population [34]. Genetic factors also partially explain the higher risk of autoimmune disorders in PSC, as there are shared susceptibility genetic loci with celiac disease and type 1 diabetes mellitus, among others [24,35].

PSC is generally more prevalent in men, with a roughly 1.8:1 male-to-female ratio, but the subtype of PSC-IBD is probably more in females, with a ratio of 1.5:1 [5,36]. The median age of PSC diagnosis is 40 years, compared with 33 years for IBD [5,36]. Another incidence peak at age 70 years has been described in Asia, but not in European or Northern American countries, with IGG4-related cholangitis as a potential confounder [28,29,36]. About 6% of all PSC diagnoses occur in pediatric populations, with a peak age of 12.3-14.6 years, and these patients still demonstrate similar sex and IBD subtype distributions as adult-onset PSC [37].

Pediatric-onset PSC also has similar rates of complications, CRC incidence and requirement for LT as adult PSC [38].

Among patients with IBD, PSC may occur in 2-14% of patients with UC and 1-8% of those with Crohn's disease (CD) [1,3,37,39,40]. Conversely, up to 80% (range 40-98%) of patients with PSC have a diagnosis of IBD, also influenced by geographical distribution [3,6,36,41]. Part of the wide estimate range may be explained by an insufficient workup of IBD when PSC is diagnosed. Most cases are diagnosed either within the first decade after IBD diagnosis, or at the same time [36,42,43], and a minority (about 16%) of patients have PSC established before IBD. In some cases, the diagnosis of IBD is after LT [36].

Clinical presentation and natural history

The most common prevalent symptoms of PSC are pruritus, fatigue and brain fog, although right upper quadrant abdominal pain and nausea can also be frequent. The PSC Support Patient Insights Survey (Part 1 - Living with PSC) was written by PSC Support and published on 5 May, 2020 (https://www.pscsupport.org.uk/insights-living-with-psc). Some patients, however, may be diagnosed after asymptomatic cholestatic liver enzyme elevation.

PSC trends with or without IBD

A few studies have looked into the natural history trends that differentiate patients with PSC-IBD and those without IBD (Fig. 1). A study conducted in an Australian cohort found no statistical differences in demographics (age, sex, bile duct involvement, subtypes of PSC) among PSC patients with or without IBD. However, patients with IBD had a higher incidence of gastrointestinal malignancies (22% vs. 2%, P<0.01) compared to those without IBD, and a higher mortality rate, being solely in the PSC-IBD cohort (21% vs. 0%, P<0.01) [44]. The higher mortality was driven more by cholangiocarcinoma (CC) rather than liver failure. However, there were no significant differences in LT rates or transplant-free survival between the 2 groups [45]. Another study indicated that PSC patients with CD had a more favorable outcome compared to those with UC or without IBD. Specifically, PSC/CD patients had less progressive liver disease and better LT-free survival rates [46]. PSC patients without IBD tend to have a faster progression to liver cirrhosis and dominant stenoses. A third study found that isolated PSC patients had significantly later diagnoses of PSC (39 vs. 28 years, P=0.02), earlier diagnoses of dominant stenoses (29 vs. 74 months, P=0.021) and faster progression to liver cirrhosis (38 vs. 103 months, P=0.027), compared to PSC patients with IBD [47]. Similarly to other studies, CRC rates were higher in the concomitant PSC and IBD group (8.7% vs. 0%, P=0.042) which also had numerically higher mortality (10% vs. 5%). In summary, PSC patients with IBD have a higher risk of malignancies and overall mortality (driven more by malignancy rather than liver failure), while those without IBD experience faster disease progression to cirrhosis and dominant stenoses. These differences underscore the need for tailored surveillance and management strategies in PSC patients based on their IBD status.

Table 1 Mayo model for predicted survival in primary sclerosing cholangitis

Model R = 0.03 (age [yrs]) + 0.54 $\log_e$(bilirubin [mg/dL]) + 0.54 $\log^e$(AST [IU/L]) + 1.24 (variceal bleeding [0=no/1=yes]) - 0.84 (albumin [g/dL]).]

Survival function coefficient [$S_0(t)$]*
1 year = 0.963
2 years = 0.919
3 years = 0.873
4 years = 0.833
Calculated patient survival
Probability of survival at time t years is calculated as $S(t)= S_0(t)^{exp(R-1.00)}$

*$S_0(t)$ gives the estimated survival probabilities for a patient with a risk score of 1.00, which is the approximate risk score of the average patient in the data set. To calculate the probability of survival at t years of a given patient, use the following equation: $S(t)= S_0(t)^{exp(R-1.00)}$

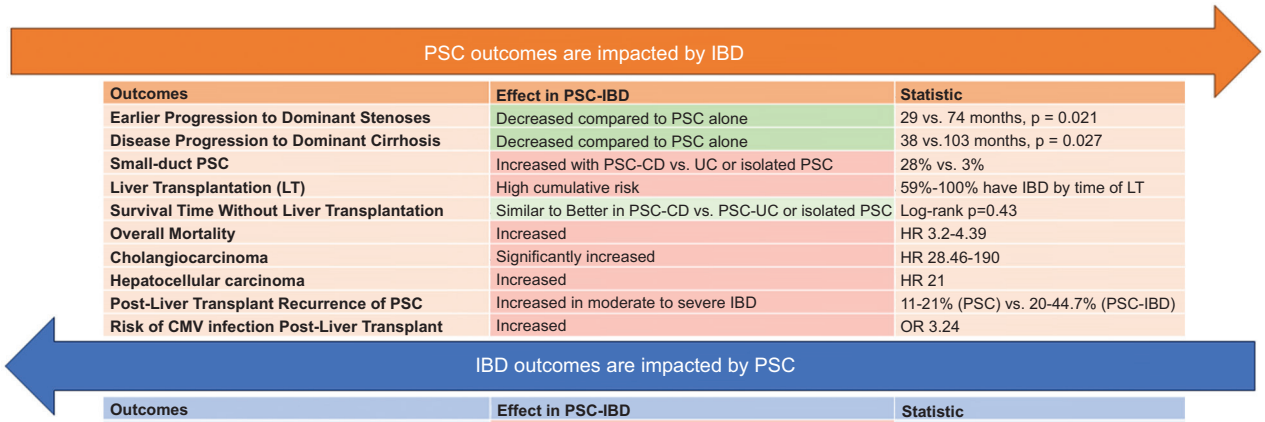
An online calculator for the revised model is available at https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/the-revised-natural-history-model-for-primary-sclerosing-cholangitis/itt-20434725

AST, aspartate aminotransferase

Classification of "PSC-IBD"

As previously mentioned, IBD in PSC is different phenotypically from classic UC or CD alone, and many have coined "PSC-IBD" as a unique phenotype, even though no clear immunophenotype difference exists [10]. This typically presents as pancolitis with worse endoscopic disease in the right colon, and has mild inflammation histologically, with some skip lesions [25,36,43,48-50]. In CD-like disease, the extent is more commonly colonic or ileocolonic, and isolated ileal disease is rare [3,36,49,51]. In UC-like disease, an active inflammation that decreases more distally with eventual rectal sparing, as well as the occurrence of backwash ileitis, are considered typical in PSC-IBD [3,36]. However, owing to the poor definition consensus of either backwash ileitis or rectal sparing, too many studies have found mixed results for these findings to be truly considered pathognomonic [43,52-54].

Patients with PSC-IBD often have discrepancies between the location and severity of histopathologic and endoscopic inflammation, necessitating histopathology sampling in all quadrants of the colon and the terminal ileum [49]. Inflammatory histopathology changes are predominantly mild-to-moderate and worse in the right colon. Both right-sided disease and mild histo-endoscopic findings have been postulated to correlate with lesser clinical symptoms in patients with PSC-IBD compared to IBD alone [55].



Outcomes	Effect in PSC-IBD	Statistic
Earlier Progression to Dominant Stenoses	Decreased compared to PSC alone	29 vs. 74 months, p = 0.021
Disease Progression to Dominant Cirrhosis	Decreased compared to PSC alone	38 vs.103 months, p = 0.027
Small-duct PSC	Increased with PSC-CD vs. UC or isolated PSC	28% vs. 3%
Liver Transplantation (LT)	High cumulative risk	59%-100% have IBD by time of LT
Survival Time Without Liver Transplantation	Similar to Better in PSC-CD vs. PSC-UC or isolated PSC	Log-rank p=0.43
Overall Mortality	Increased	HR 3.2-4.39
Cholangiocarcinoma	Significantly increased	HR 28.46-190
Hepatocellular carcinoma	Increased	HR 21
Post-Liver Transplant Recurrence of PSC	Increased in moderate to severe IBD	11-21% (PSC) vs. 20-44.7% (PSC-IBD)
Risk of CMV infection Post-Liver Transplant	Increased	OR 3.24

Outcomes	Effect in PSC-IBD	Statistic
Colonic Involvement (UC-like disease)	More extensive phenotype	68-78% inPSC-IBD vs. 44% in IBD
Ileal involvement (CD-like disease)	Rare	0-5% PSC-CD vs. 33% in CD
Backwash ileitis	Similar to Increased	RR 0.7 (0.4-1.4) - 13.5 (3.2-57.6)
Rectal Sparing	Similar to Increased	RR 1.5 (0.3-8.7) - 24 (3-180)
Resective Surgery,Mainly Colectomy	Similar to Increased; less with severe PSC needing LT	HR 2.13
Pouchitis	Increased	OR 4.21 (acute)-6.37 (chronic pouchitis)
Pouch Failure	Increased	OR 1.85
Colorectal Cancer	Increased rate and younger onset	HR 3.41-21.4, more in UC vs. CD

Figure 1 Bidirectional impact of primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) on their respective outcomes
CD, Crohn's disease; UC, ulcerative colitis; HR, hazard ratio; OR, odds ratio; RR, relative risk

Small-duct PSC

Small-duct PSC, historically called pericholangitis, is a rare subtype of PSC, representing 3.6% of all PSC cases [6]. It shares the demographic, laboratory and histopathologic findings of large-duct PSC, but the radiological findings are absent or inconsistent with PSC [6]. Small-duct PSC is more prevalent in PSC patients with CD compared to those with UC or without IBD (28% vs. 3%) [46]. Conversely, a systematic review noted that large-duct PSC patients had a higher prevalence of IBD (odds ratio [OR] 2.57, 95% confidence interval [CI] 2.03-3.25) and UC (OR 4.51, 95% CI 1.22-16.71) than small-duct PSC patients [2]. Small-duct PSC patients had markedly better survival than large-duct PSC: in 1 study, no patient developed CC or liver-related death, but a few still developed CRC [46]. It is worth noting that up to 55% of patients with small-duct PSC may develop cholangiographic evidence of large-duct PSC with time [56].

Complications

Luminal complications

Despite its seemingly mild-to-moderate presentation, patients with PSC-IBD still carry high rates of colectomy and require intensive treatments [4,49], yet the true effect of PSC on colectomy rates is debatable [57]. This is in part due to the higher risk of dysplasia and CRC in this population [39,58,59], which is 7 times that of the general population [60], and 3-5 times that of UC alone [58,59]. In The Netherlands, PSC patients with CRC had concomitant IBD in 95% of cases [30]. Besides PSC, risk factors for CRC include extensive colitis, UC subtype, chronic inflammation, presence of low-grade dysplasia, inflammatory polyps, and a family history of colorectal cancer [61]. CRC in PSC-IBD tends to occur at a younger age than in those with IBD alone [4]. It is theorized that, because of its milder phenotype, active inflammation goes unchecked for a longer time [42], and that dysplasia has already ensued by the time of (or shortly after) diagnosis, underscoring the need for yearly screening protocols as soon as PSC-IBD is diagnosed [7,62].

Patients with PSC-IBD, especially the UC-like phenotype, undergo more total colectomy with restorative pouch surgery than their UC counterparts [10,52]. Given the greater risk of neoplasia and dysplasia, total vs. subtotal colectomy has been favored; however, recent surveillance studies suggest that subtotal colectomy in patients with rectal sparing and regular endoscopic surveillance may be a viable option [63]. Antibiotic-refractory pouchitis is also more common in patients with PSC-IBD compared to UC alone, underscoring the potential effects of PSC on the pouch [64]. A confounding factor here is the higher prevalence of backwash ileitis in patients with PSC-IBD, another known risk factor for pouchitis [65].

Hepatobiliary malignancy

Patients with PSC are at increased risk of developing hepatobiliary malignancies, carrying a lifetime risk of 4.5-15% [6,29,30], particularly with CC, as high as 8.1 per 1000 person-years, compared to no CC in matched controls from the general population [66]. This equates to a more than 200-900 times greater risk of CC compared to the general population [29]. The mean time from PSC to CC diagnosis is

3.3-6 years, and the mean time from CC diagnosis to death is 1.8 years [29,30,67]. CC may be diagnosed synchronously with the PSC diagnosis in up to 10% of patients [68]. CC may also be discovered during LT in up to 30% of cases [69]. CC carries a high mortality rate, with 1-year survival rates of 20-25% [30]. Risk factors associated with CC are older age at PSC diagnosis, longer duration of IBD before PSC diagnosis [68], smoking [70], a history of variceal bleeding [67], and history of CRC [30]. CC associated with PSC can occur both extrahepatically (primarily proximal biliary tree such as hilum or common hepatic duct, although cystic duct can occur) and intrahepatically. Dysplasia in a non-CC biopsy site can be detected in up to 60% of cases [70]. The distribution of PSC did not predict an increased risk of CC [70].

Gallbladder cancers (1-3%) and, to lesser extent, hepatocellular carcinomas are also reportedly more likely in patients with PSC, with standard incidence ratios of 78 (21-200) and 22 (4-63), respectively, compared to the general population [29,71,72]. Interestingly, pancreatic cancer rates were not different from the general population [29,66].

Cirrhosis and LT

Cirrhosis and liver failure may be diagnosed in up to 6.4% of patients at the time of PSC diagnosis, and end-stage liver disease (ESLD) is prevalent in 19-37% of all PSC patients [28,73,74]. Incident cirrhosis and portal hypertension rates over time are estimated at 18.6 and 14.5 per 1000 person-years, respectively [66]. Almost half the patients with ESLD undergo LT, compared to 5-16% of all PSC incomers [30,66,73,75,76]. Besides ESLD, the most common indication for LT in PSC is CC. Transplant-free survival was estimated at 65% over 10 years in 1 study, but was 94.04% and 81.63% at 10 and 20 years, respectively, in another [73,74]. Interestingly, some data suggest that more progressive PSC leading to LT is associated with a more attenuated form of IBD, and worse colitis may also dampen the progression of PSC to LT [18,19].

Mortality

Data from a single tertiary center reported shorter median times to death (all-cause) or LT compared to national population-based studies (9.74 vs. 20.6 years) [28]. The median interval between PSC diagnosis and PSC-related death ranged from 14.5-21.4 years, and was largely driven by decompensated cirrhosis and malignancy, primarily CC [6,30]. Indeed, liver-related deaths accounted for 46-100% of all-cause mortality across studies [66,73,74,76]. Among cancers, death from CC is more common than death from CRC [30]. Compared to age- and sex-matched controls without liver disease, the adjusted hazard ratio for LT or death was estimated at 3.56 (95%CI 2.69-4.72) [75]. At a mean age of 40 years for PSC diagnosis, the 10-year relative survival ratio was 93%, and this decreased to 77% for a mean age of diagnosis of 54 years [28,29,66].

A multivariable analysis suggested that age at PSC diagnosis and development of CC were predictive of PSC-related death, whereas patient sex, IBD comorbidity, autoimmune hepatitis, colectomy, CRC, LT, PSC morphology (small-duct), or ursodeoxycholic acid levels showed no similar predictive ability [30]. In comparison, 2 Northern American studies corroborated the relationship between advanced age and PSC-related death or LT, but serum biomarkers (mainly liver biochemistry) were also useful predictors [74,76].

Workup and prognostication

The diagnosis starts with a high index of suspicion based on elevated cholestatic liver enzymes and clinical symptoms suggestive of cholestasis, and further heightened in a patient with comorbid IBD. In patients with new symptoms, the majority are diagnosed within 3 months, according to the PSC Support Patient Insights Survey (https://www. pscsupport.org.uk/insights-living-with-psc). However, as many as 8-14% of patients may be diagnosed incidentally on cross-sectional imaging before cholestatic disease is evident clinically or on laboratory testing [1,77]. Routine liver biopsies in patients undergoing IBD surgery have shown evidence of PSC in up to 13% [78].

Liver biochemical tests predominantly reflect a cholestatic pattern, with a notable elevation of serum alkaline phosphatase (ALP). Serum ALP and bilirubin do fluctuate, reflecting the transient blockage of strictured bile ducts by biliary sludge or small stones. Serum aminotransferases are usually less than 300 IU/L. The serum albumin may be low in patients with active IBD or ESLD. Other serologic findings include elevated hypergammaglobulinemia (up to 30%) and serum immunoglobulin M (40-50%), and atypical perinuclear antineutrophil cytoplasmic antibodies (30-80%). Other autoantibodies and biomarkers may exist with unclear significance, such as antinuclear, anti-smooth muscle, anticardiolipin and serum immunoglobulin G4 (IgG4) [79].

Magnetic resonance cholangiography is the ideal initial noninvasive test for diagnosis, with sequential intrahepatic and extrahepatic dilated and stenotic bile ducts that appear like beads on a string [80]. A rare subtype of PSC may not showcase these features, but instead is diagnosed microscopically as small-duct PSC. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography are other, more invasive procedures that were historically used for diagnosis purposes. However, owing to their invasive nature, along with the risk of infection and radiation exposure, these modalities are not preferred diagnostic tools.

Secondary causes of sclerosing cholangitis should be excluded, namely IgG4-associated cholangitis, sarcoidosis, recurrent pyogenic cholangitis, drug-induced liver injury, septic cholangiopathy and CC [10]. In patients with mixed or

Table 2 Models for management of primary sclerosing cholangitis (PSC)

Model	Components	Advantage	Disadvantage
Alkaline phosphatase	Serum ALP	• Simple serum test • Correlates with disease progression • Used in PSC trials as outcome	• Natural history of fluctuation in PSC • Sensitive to other biliary complications (cholangitis, gallstones, dominant stricture, CCA)
Mayo Risk Score (MRS)	Age, bilirubin, serum AST, serum albumin, and history of variceal bleeding	• Does not include invasive or subjective parameters • Variables correlate with advanced liver disease	• Inadequate discriminatory function in early-stage PSC • Predictable time period for 4 years only
Amsterdam-Oxford model (AOM)	PSC subtype, age at diagnosis, platelet count, serum albumin, ALP, AST, and bilirubin levels	• Generalized PSC population dataset with long-term data (15 years) • Allows for recalculation at later timepoint • Overcomes limitations of MRS in relation to transplant-free survival	• Only moderate discriminatory power (C-statistic 0.68)
UK-PSC scores	Serum bilirubin, ALP, albumin, platelets, presence of extrahepatic biliary disease, and variceal hemorrhage	• Validated Modeling for 2- and 10-year timepoints • Predicts transplant-free survival better than MRS	• 10-year prediction requires data from 0 and 2 years timestamps.
PSC risk estimate tool (PREsTo)	Bilirubin, albumin, serum ALP times the upper limit of normal, platelets, AST, hemoglobin, sodium, patient age, and number of years since the diagnosis of PSC	• Predicts hepatic decompensation better than MRS or MELD	• Individuals with advanced PSC or CCA at baseline were excluded • Online calculator, proprietary formula.
Enhanced liver fibrosis test	Based on purely serological measurements summarizing 3 direct components of fibrogenesis (hyaluronic acid, tissue inhibitor of metalloproteinase 1, and type III procollagen amino-terminal propeptide)	• Strong predictor of mortality and liver transplantation • Validated results over 5-year period	• Availability and coverage

Adapted from Tornai, David et al "Serological biomarkers for management of primary sclerosing cholangitis." *World J Gastroenterol* 2022;28: 2291-2301. doi:10.3748/wjg.v28.i21.2291

ALP, alkaline phosphatase; AST, aspartate aminotransferase; MELD, model for end-stage liver disease; CCA, cholangiocarcinoma

hepatotoxic hepatic panels, liver biopsies in IBD patients may be useful for elimination of other diagnoses, such as primary biliary cholangitis or other autoimmune liver diseases.

In patients without prior diagnosis of IBD, a colonoscopy with random biopsies at PSC diagnosis is recommended by international guidelines [7,8]. Histological inflammation can be more frequent than endoscopic findings, especially in asymptomatic patients [49].

The Mayo Risk Score

Among multiple predictive models for PSC, the Mayo Risk Score stands out as a well-validated statistical model that incorporates variables associated with PSC survival, and can aid in liver transplantation planning. These variables are age, bilirubin, serum aspartate aminotransferase, serum albumin, and a history of variceal bleeding [81] (Table 1). The score, in its revised form, avoids the use of histologic stage (not available in some patients) and factors with subjective definitions, such as splenomegaly. Other models exist and exhibit different strengths and disadvantages to the Mayo Risk Score (Table 2) [82].

Management

Rocky journey to therapeutic discovery

Given that bile acid metabolism, colonic permeability through IBD-mediated inflammation, lymphocyte trafficking aberration and gut dysbiosis have all been postulated in the pathogenesis of PSC, agents that impact these pathways have been assessed for its management. Unfortunately, there is a lack of strong evidence to approve any single agent in the treatment of PSC. For example, studies evaluating therapies that impact T lymphocyte aberrant trafficking, such as the use of VAP1 antibody timolumab [83] and vedolizumab [84,85], did not reveal clinically significant improvements.

The dysbiosis theory in PSC generated many studies investigating the effects of antibiotics. Vancomycin and, to a lesser extent, metronidazole showed particularly beneficial effects on the Mayo PSC Risk Score and ALP levels in patients with PSC-IBD [86,87]. Fecal microbiota transplantation (FMT) data in PSC are scarce, with only a small pilot study involving 10 patients suggesting a potential beneficial effect on biochemical markers in PSC [88].

Given the shared genetic pathways with celiac disease, a gluten-free and amylase trypsin inhibitor-free diet for 8 weeks

Table 3 Currently active and recruiting interventional trials in primary sclerosing cholangitis (PSC) based on clinicaltrials.gov, accessed January 13, 2025

Trial Name	Drug	Phase	Mechanism of action	Primary outcome
ALPINE-PSC-NCT06654726	Aldafermin	IIb/III	Action on liver steatosis and insulin sensitivity via FGFR1c-KLB and FGFR4-KLB receptors	Change in fibrosis biomarkers (ELF score)
NCT06699121	LB-P8	II	Live biotherapeutic product consisting of a single bacterial strain (Leuconostoc citreum), modulates the gut microbiome, specifically by influencing bile acid metabolism	Treatment-related adverse events Mean percent change from baseline in serum concentrations of ALP
NCT05642468	A3907 (Ritivixibat)	II	Systemic ASBT inhibitor; improves cholestatic disease	Treatment-related adverse events
NCT03561584	Sulfasalazine	II	Inhibits the transcription of pro-inflammatory genes that are responsive to NF-κB, TNF-α and reduces bacterial growth	Treatment-related adverse events Reduction in serum ALP and other biomarkers of liver injury
NCT05896137	CS0159 (Linafexor)	II	Potent agonist of the farnesoid X receptor (FXR), regulating bile acid metabolism and inflammation	Treatment-related adverse events Reduction in serum ALP and other biomarkers of liver injury
HAAPS Study NCT05295680	Hymecromone	II	Inhibitor of hyaluronic acid synthesis	Change in serum GGT levels
NCT04133792	Simvastatin	III	Statin, inhibits the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase	Overall and LT-free survival
VISTAS - NCT04663308	Volixibat (VLX-301)	II	Selectively inhibits ASBT in the small intestine, preventing the reabsorption of bile acids	Mean change in the daily itch scores
DOLPHIN - NCT05835505	BRS201	II	Unknown	Normalization of serum ALP
NCT06197308	Oral microbiota transplant therapy	I	Restoration of gut dysbiosis	Safety and feasibility of microbiota therapy
NCT06026865	S-adenosylmethionine	NA	Ameliorates oxidative stress and inflammation	Change in liver biochemistries Change in quality of life
BEZASCLER - NCT04309773	Bezafibrate	III	Activates PPARα, a nuclear receptor protein, regulates the expression of genes involved in lipid metabolism	Reduction in serum ALP
NCT02137668	Vancomycin	I	Antibiotic, cell wall synthesis inhibitor	Blood tests, imaging studies and/or liver biopsy changes
NCT06351696	Bromelain/Low FODMAP diet	NA	Protease enzyme found in pineapple that can reduce inflammation and pain	Simple clinical colitis activity index questionnaire
FARGO - NCT06286709	Fecal microbiota transplantation	II	Restoration of gut dysbiosis	Reduction in serum ALP
NCT05912387	Rosuvastatin	I	Statin, inhibits the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase	Change in bile acid profile
VanC-IT - NCT05876182	Vancomycin	II	Antibiotic, cell wall synthesis inhibitor	Reduction in serum ALP
NCT06026449	Gluten-free diet	NA	Reduce immune-mediated damage related to gluten	Reduction in serum ALP
SET-SAIL - NCT06455280	Siplizumab	I	Anti-cluster of differentiation 2 monoclonal antibody	Serious infection in the first month post-transplant Incidence of immune-mediated liver injury

ASBT, apical sodium-dependent bile acid transporter; ALP, alkaline phosphatase; ELF, Enhanced Liver Fibrosis; GGT, γ-glutamyltransferase; LT, liver transplantation; NA, not applicable; PPARα, peroxisome proliferator-activated receptor alpha

was investigated, but had no clinical effect on PSC or IBD. However, proinflammatory and profibrosis markers were downregulated, suggesting some linkage between diet and PSC that may need interventions of longer duration to show a true clinical benefit [89].

Thus, longer follow-ups with more clinically useful endpoints are needed to justify the long-term use of antibiotic, FMT or dietary interventions in this population. Currently active clinical trials for PSC are summarized in Table 3.

Current best practice

Ursodeoxycholic acid (UDCA)

Despite animal models and early trials suggesting a benefit from secondary bile acids such as UDCA or obeticholic acid on liver biochemistry [22,86,90], long-term use of UDCA did not impact prognosis beyond biochemical cholestasis, apart from 1 Japanese study [10,91]. The use of UDCA was not significantly associated with a lower rate of PSC-related death in multivariate analysis [30,74]. This translates into conflicting international professional organization recommendations on its use in PSC [7,8,92]. The American College of Gastroenterology (ACG) and the American Association for the Study of Liver Diseases (AASLD) guidelines recommend that UDCA at doses of 15-20 mg/kg/day could be tried, and maintained if liver biochemistry or clinical relief is noted, although the effects on long-term prognosis remain unclear [71,92,93]. These recommendations are based on evidence suggesting that while high doses of UDCA (28-30 mg/kg/day) are associated with adverse outcomes [94], moderate doses (15-20 mg/kg/day) may offer biochemical improvement and potential clinical benefits, without the same level of risk. The ACG and AASLD guidelines emphasize that this approach should be considered in the context of individual patient response and clinical judgment.

Fenofibrate

Fibrates confer anticholestatic effects in PSC through their action on peroxisome proliferator-activator receptors. Similarly to UDCA, fenofibrates can improve cholestatic biochemistry and symptoms, especially in combination with UDCA or in UDCA partial responders [95,96], but they have not been proven to improve LT-free survival.

Pathway to LT

Patients are followed routinely in hepatology clinics for monitoring biochemistry, liver fibrosis via measurements of liver stiffness, and surveillance of complications (hepatocellular carcinoma, cholangiocarcinoma, CRC, cholangitis, dominant biliary strictures). Patients have a higher risk of cholangitis, also requiring hospitalizations and biliary interventions; current guidelines exist on the best practices for such interventions [97,98]. Patients with PSC should be advised that adverse events post-ERCP are higher than in the general population (7-18% vs. 3-11%), largely owing to post-ERCP pancreatitis and post-ERCP cholangitis [97].

While evaluating for LT, it is worth noting that survival outcomes (both patient and graft) are better in living-donor liver transplants compared to deceased-donor liver transplants; this is similar to other LT indications [99].

Effects of IBD management on PSC outcomes

Few studies have investigated the impact of advanced IBD therapies on PSC outcomes such as LT-free survival. A Swedish national registry showed lower rates of LT and mortality with azathioprine use, but this effect was not seen by another French study [100,101]. Other observational studies, and 1 small randomized controlled trial, failed to show positive effects for other IBD agents, such as mesalamine, tumor necrosis factor alpha inhibitors and vedolizumab, even in the pediatric population [84,85,101-103]. Only 1 small multicenter study investigated tofacitinib, with potential effects on liver biochemistries; these need to be replicated in larger populations [104]. These types of studies are difficult to conduct, given the lack of good surrogate markers for the early progression of PSC. Improvement or stabilization of ALP or γ-glutamyl transferase levels is most commonly used as a surrogate, but it should be kept in mind that there are considerable natural variations in ALP levels in PSC, and that even advanced disease can present with normal ALP levels [74]. Overall, no clear evidence supports the notion of tight IBD control to impact the progression of PSC. Nevertheless, some studies suggest that uncontrolled IBD could portray a severe phenotype where PSC might progress the fastest [102]. A deeper understanding of the pathological link between PSC and IBD is needed to uncover better treatment strategies.

The data surrounding the impact of colectomy on PSC outcomes are controversial; study limitations include small patient numbers, confounded by unobserved risk factors and not considering colectomy as a time-dependent covariate. One study showed no increased risk of developing PSC among patients with UC who underwent colectomy vs. those who did not [105]. LT-free survival was improved, however, in patients with a colectomy that occurred prior to PSC diagnosis, compared to patients with intact colons at PSC diagnosis; colectomy after diagnosis had no impact on LT-free survival [57]. A recent large population-based Dutch study used colectomy as a time-dependent variable, and concluded that colectomy with permanent ileostomy offers the most protective LT-free survival effect (hazard ratio [HR] 0.47, 95%CI 0.24-0.93), but the presence or absence of IBD did not affect LT-free survival [106]. No data were provided on whether colectomy occurred prior to the PSC diagnosis. Despite these results, ileostomies, mainly Brooke's ileostomies, have not been favored given concerns over stomal varices, and perhaps because of the generally younger patient population with preference to avoid

stomas [57]. A Swedish population-based nationwide cohort study, including all patients with UC, suggested that the chance of restorative surgery in PSC-UC patients is higher than in UC alone (51% vs. 41%). Interestingly, ileorectal anastomoses (IRA) were more common in PSC-UC patients compared to UC alone (63% vs. 43%), whereas the opposite was true for ileal pouch-anal anastomosis (IPAA) (35% vs. 55%), yet technical failure rates of restorative surgeries were numerically higher (16% vs. 13%, HR 1.44, 95%CI 0.93-2.22) in those with PSC-UC compared to UC alone [107]. Interestingly, IRA was more common than IPAA, probably because of rectal sparing in PSC-UC. A systematic review and meta-analysis found that patients with PSC and UC were significantly more likely to experience pouch failure compared to those with UC alone, with an OR of 1.85 (95%CI 1.08-3.17) [108]. Additionally, patients with PSC-IPAA had poorer functional outcomes and a higher incidence of acute pouchitis compared to UC-IPAA, which can contribute to long-term pouch failure [109]. Furthermore, patients with PSC had more frequent and severe episodes of pouchitis, which is a known risk factor for pouch failure [110]. These findings collectively highlight the greater risk of pouch failure in patients with PSC undergoing IPAA. A recent study challenges the notion that total colectomy is necessary, and suggests that subtotal colectomy with IRA may carry no additional risk of dysplasia/neoplasia under regular endoscopic surveillance [63]. This study also reflects more recent trends for more IPAA surgeries compared to IRA or ileosigmoid anastomosis in tertiary centers, yet potentially with higher surgical complication rates (7.5 vs. 2.7 per 100 years). Data suggest that the risk of pouchitis is higher in patients with PSC-IBD who get a J-pouch created prior to LT, compared to those with post-LT J-pouch creation [111].

Vancomycin and PSC

A particular interest in vancomycin and PSC-IBD was first described in 1998 [112]. Oral vancomycin was associated with improved liver biochemical tests and symptoms in a pilot observational study of 14 children with PSC, particularly in those without cirrhosis [113]. One of the patients had notable improvement in histology 2 months after treatment. Subsequently, in a randomized trial of 35 PSC patients comparing 12-week courses of vancomycin (125 or 250 mg q.i.d.) vs. metronidazole (250 or 500 mg t.i.d.), a decrease in ALP was seen in patients who received vancomycin, and the Mayo Risk Score decreased in those who received low-dose vancomycin or low-dose metronidazole [114].

An open-label study of oral vancomycin treatment of 59 children and adults with PSC reported 81% and 22% reduction and normalization of ALP, respectively, over 2.7 years [115]. However, a larger 1:1:1 matched retrospective analysis of the pediatric PSC consortium showed no improvement in outcomes (biochemistry normalization, liver fibrosis stage changes, or LT rates at 5 years) between 88 children on oral vancomycin, when matched with 88 children on UDCA or 88 others with no treatment strategy [116].

Vancomycin's effects on the IBD component of PSC-IBD may be more promising. Multiple case reports and case series depict improvement in clinical and endoscopic findings of IBD post-vancomycin treatment (usually doses of 125 mg q.i.d., tapering to a less frequent regimen 4-8 weeks later) [117-119]. These patients often failed prior IBD therapies, including mesalamine, immunomodulators and biologics. The impact was noted even in post-LT patients with normal biochemistry [120], or in patients with IPAA restorative surgery [121], suggesting dysbiosis changes particular to PSC-IBD that persist despite LT or colectomy.

Post-transplantation PSC-IBD considerations

There is ongoing debate on the natural history of IBD post-LT, with studies favoring both improvement or worsening of luminal activity [49,122,123]. In patients with PSC alone, *de novo* IBD could occur in 18% of patients during the first decade post-LT [25]. LT immunosuppressive medications seem to affect the rate of IBD flares, with higher rates of *de novo* IBD and exacerbations in patients treated with tacrolimus/mycophenolate mofetil compared to cyclosporin/azathioprine [124]. Conversely, LT in patients with IBD may carry a higher risk of rejection compared to non-IBD patients, especially if IBD is active at the time of LT [9,125,126]. Moderate-to-severe IBD post-LT is associated with a greater risk of acute cholangitis, biliary strictures and recurrent PSC (rPSC), but also worse IBD outcomes (dysplasia, CRC and colectomy), compared to no or mild active IBD [9]. In the acute postoperative period, active IBD may predispose patients to higher thromboembolic risk, particularly hepatic artery thrombosis [127].

Rates of rPSC range from 10-25%, but biliary stricture in the transplanted liver may be ischemia-induced yet mistaken for rPSC [10]. IBD is an independent risk factor for rPSC, but interestingly, colectomy pre-LT is associated with lower rates of rPSC and better graft survival [128,129]. The effect of colectomy, however, is not present in all studies [122,125,126]. The type of colectomy was investigated, and total colectomy with permanent ileostomy (either pre- or post-LT) was found to carry a protective effect compared to IPAA [129,130].

We feel that it is essential to combine advanced IBD therapies and immunosuppressive LT medication in a fashion that both controls IBD and prevents rejection, while closely monitoring patients to prevent significant adverse events [131].

CRC surveillance considerations

Guidelines recommend yearly colonoscopy for the surveillance of dysplasia and CRC in all patients with PSC and IBD, starting at the time of PSC diagnosis. In the absence of IBD, surveillance is currently recommended at 5-year intervals [7,62]. Effective surveillance strategies have shown a decrease in rates of CRC in patients with PSC-IBD. Deaths related to CRC are also fewer in surveilled compared to non-surveilled patients (53%

vs. 16%) [30]. Intensified surveillance is still required, even after LT, because of the continuing higher risk of CRC [132]. Owing to the concern of atypical, invisible and multifocal lesions of dysplasia in PSC-IBD, chromoendoscopy or high-definition white-light endoscopy with random and targeted biopsies have been suggested [133,134]. Colectomy is recommended for endoscopically non-resectable high-grade dysplasia or CRC, or multifocal invisible low-grade dysplasia [7,62].

Concluding remarks

PSC is a chronic cholestatic liver disease characterized by chronic inflammation and progressive fibrosis of the biliary tree. Although the majority of patients with PSC have concomitant IBD, the interaction between both disease entities needs further exploration. Guidelines recommend vigilance in detecting PSC in patients with IBD, and screening for IBD when PSC is first detected. Similarly, regular screening for CC and for progression to ESLD aid in timely referral for LT. Patients with PSC-IBD carry a high risk of dysplasia and CRC, for which yearly colonoscopic surveillance protocols are implemented.

The lack of effective treatments for PSC reflects the challenges in diagnosis as well as our limited understanding of the pathophysiology of the disease. Strategies towards early detection of PSC in individuals at high risk may aid in studying possible therapeutic agents at earlier PSC stages, before irreversible bile duct damage ensues. This requires the discovery of PSC-specific biomarkers (chemical, multi-omic or image-based) that are sensitive to early disease changes. Specific PSC-IBD patient subgroups stand out as potential candidates for research to better understand the interplay of pathophysiology in PSC and IBD. Colectomized patients can be prospectively followed to further elucidate whether abolishing portal vein translocation of immunological or microbiological pressures has an impact on PSC. Transplanted and colectomized patients might be the best model, given the ability to detect early signs of rPSC as a surrogate to early PSC pathogenesis. Similar research could be conducted to assess the impact of colectomy on the generation of aberrant gut-homing lymphocytes. Comparing patients with partial and total colectomy could be a separate model. Similarly, comparing patients with or without pouchitis may unfold dysbiotic signatures in the pouch that could lead to PSC progression or rPSC in transplanted patients. Until then, achieving deep remission in IBD remains a target to be achieved, and the utilization of oral vancomycin therapy holds a particular position in this subgroup, which requires further investigation.

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