Defining Primary Sclerosing Cholangitis: Results From an International Primary Sclerosing Cholangitis Study Group Consensus Process

Primary sclerosing cholangitis (PSC) is a chronic progressive inflammatory disease of the bile ducts that is surrounded by much uncertainty. First of all, it is a rare disease, with reported prevalence between 0 and 31.7 per 100,000 individuals,[1,2] and establishing a diagnosis can be difficult. The primary pathology is hidden deep in the liver, and there is no specific and easy noninvasive diagnostic test for PSC. Histologic features of fibrosing cholangiopathy are present in <20% of liver biopsy specimens obtained from patients with PSC and can also be seen in cases of secondary sclerosing cholangitis. Current US and European guidelines do not recommend liver biopsy for making a diagnosis of PSC except for suspected cases of small duct PSC and pediatric cases.[3,4] In addition, biliary tract abnormalities can be found on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiography (ERC) in a wide array of conditions (see Supplementary Table 1). Furthermore, the course of PSC can be variable. Liver transplant–free survival ranges between 14.5 and 21.3 years in large cohorts.[5,6] An important risk factor affecting survival is the development of cholangiocarcinoma (CCA). This has a cumulative incidence of approximately 20% at 20 years after diagnosis, but one third of CCA cases become manifest within 1 year after the diagnosis of PSC.[5,6] Last but not least, the cause of PSC is still enigmatic, and consequently, there is no therapy that has been proven to modify disease progression. In recent years, there has been an upsurge of pilot studies and phase 2 clinical trials. Phase 2 and 3 trials are hampered by the lack of established surrogate endpoints for clinical outcome, the heterogeneity of the disease course, and the lack of clear definitions for many key clinical disease characteristics.[7]

While the available national and international clinical practice guidelines predominantly focus on clinical management, the International PSC Study Group (IPSCSG) has recognized that there is a vital need for clinical trials to use uniform definitions for the diagnosis of PSC and for assessing disease severity and outcomes.[3,4,8] Therefore, the IPSCSG has commissioned a consensus process among its experts to issue a set of definitions to aid clinical trialists designing much needed clinical trials. To this end, an extensive consensus process was initiated, applying a hybrid between a Delphi process and a nominal group process, as was previously used by the IPSCSG and the European Crohn's and Colitis Organization.[7,9] Where necessary, an additional survey was conducted among all IPSCSG members (see the Supplementary Methods for details). Results are presented as a comprehensive set of consensus statements (CSs) and diagnostic criteria for PSC.

Clinical Symptoms

Although patients with PSC are increasingly diagnosed at earlier stages of disease based on asymptomatic serum liver enzyme abnormalities, at least 45% of patients PSC present with symptoms on either a constant or intermittent basis, which significantly reduces quality of life.[10] Furthermore, more than 22% of asymptomatic patients may develop symptoms within 5 years. The most common clinical symptoms associated with PSC are fatigue; pruritus; right upper quadrant (RUQ) abdominal pain; and emotional distress, which may include anxiety and depression symptoms. Pruritus and abdominal pain can fluctuate dramatically, and this may be suddenly worsened because of the development of a biliary obstruction or acute bacterial cholangitis. Therefore, clinical evaluation with laboratory testing and imaging may be necessary in the event of the sudden appearance or worsening of symptoms. Emotional distress for many patients is attributable to chronic anxiety about the uncertain etiology of the disease, the lack of effective therapy, and the risk of malignancy, among others.[11]

The incorporation of clearly defined patient-reported symptoms into the design of clinical trials is both desirable from a patient-centered perspective and highly encouraged by regulatory agencies[12] (Box 1, CS 1.1). Recently, 2 such tools have emerged. One patient-reported outcome (PRO) dedicated to PSC showed excellent reliability and was able to discern patients with cirrhosis and those with a history of depression.[13] A more recently developed tool to assess patient-reported symptoms, the Simple Cholestatic Complaints Score, was developed through digital surveys of patients and showed good criterion and construct validity and a very high test-retest reproducibility.[14] Further validation of these tools in larger and more diverse cohorts is needed.

A particular challenge in assessing clinical symptoms in patients with PSC is the frequent concurrence of inflammatory bowel disease (IBD), which itself can influence the clinical course of PSC and may also account for a significant proportion of symptoms, especially during periods of IBD exacerbations.[15] Existing tools, including the PSC PRO, do not specifically account for symptoms attributable to IBD. Although the Simple Cholestatic Complaints Score did not show a difference in PSC patient symptoms according to the presence or absence of IBD, a systematic evaluation of IBD symptoms in patients with PSC has not been performed, which can result in confounding findings. Therefore, assessment of PSC symptoms should be performed alongside specifically designed tools to detect symptoms from IBD in those with PSC-IBD or other relevant coexistent conditions

(Box 1, CS 1.2) This is critically important for clinical trials that aim to use PRO measures as endpoints in PSC.

Laboratory Markers

Cholestatic serum liver tests are a characteristic, but nonspecific, feature of biliary disease irrespective of the nature of biliary involvement. Alkaline phosphatase (ALP) as the hallmark of cholestasis is elevated in the vast majority of patients with PSC.[16] Previously, it was thought that to make a diagnosis of PSC, elevation of ALP, or gamma-glutamyl transpeptidase (gGT) in children (see the "Pediatric Primary Sclerosing Cholangitis" section) was a prerequisite. Recent studies have shown that elevated cholestatic serum parameters need not always be present. For more background, see the Supplementary Material.

Aminotransferases are often moderately elevated, whereas at diagnosis, serum bilirubin and albumin levels are usually normal.[3] Aminotransferase activity of more than 5 times the upper limit of normal (ULN) and a serum IgG of $>2 \times$ ULN should raise the suspicion of coexisting autoimmune hepatitis (AIH) and should trigger consideration of liver biopsy to identify histologic features that would support a diagnosis of AIH or PSC/AIH overlap, also called *variant syndrome* (Box 1, CS 2.1). This has management consequences, because patients with PSC/AIH commonly respond favorably to immunosuppressive medication such as corticoids and thiopurines, although not as well as patients with isolated AIH.[17]

In contrast to primary biliary cholangitis (PBC) and AIH, there is no pattern of autoantibody reactivity in patients with PSC of relevance to diagnosis or treatment. Positive titers of autoantibodies are common in PSC, including antinuclear antibody (8%–77%), smooth muscle antibody (0%–83%), and atypical perinuclear antibody (26%–94%).[18,19] However, these are also frequently present in AIH, and perinuclear antineutrophil cytoplasmic antibodies can be found in ulcerative colitis (UC) in 41%–73% and in Crohn's disease in 6%–38%.[17-19]

Serum IgG4 levels can be elevated in patients with PSC, but this has no validated bearing on diagnosis or disease severity (Box 1, CS 2.2). For distinction from IgG4-sclerosing cholangitis, see the Supplementary Material.

Imaging

Biliary imaging is integral to the diagnosis and classification of PSC. MRCP has been established as the noninvasive imaging of choice.[3,4] Regarding the utility of magnetic resonance imaging (MRI) in PSC, the reader is referred to a recent publication from the IPSCSG Working Group on MRI in PSC.[20]

A range of cholangiographic features are described in large duct PSC, including multifocal stricturing, focal dilatation or ectasia, ductal wall thickening within the intra- and/or extrahepatic biliary tree, obliteration of the peripheral intrahepatic ducts with pruning of the biliary tree, retraction of the ampulla, and periductal inflammation. These changes are, however, not pathognomonic of PSC, and differentiation from causes of secondary sclerosing cholangitis (especially in the absence of colitis) can be difficult. Saccular outpouchings in the extrahepatic bile ducts on cholangiography are thought to be highly specific for PSC. These diverticular outpouchings in the common hepatic and common bile duct, and—very rarely—in the cystic duct, are usually seen only in advanced disease and are reported in only 7.5% of cases in a large series of ERCs.[21]

True small duct PSC where cholangiography is normal is an infrequent finding in PSC. Two recent publications have reported on the natural history of small cohorts of small duct PSC patients followed prospectively. Progression to large duct PSC was described in 33% and 55%, respectively, after a mean of 11 years of follow-up in each study[22,23] (Box 1, CS 3.1.1). There was no correlation with any baseline MRI findings and progression to large duct PSC in either study.

Dominant Strictures in Primary Sclerosing Cholangitis

Strictures in the draining bile ducts are a common and clinically relevant sequela of the chronic inflammatory process that takes place in the biliary tree in PSC. From a consecutive series of 96 large duct PSC patients followed up with regular ERCs, the incidence of the development of so-called dominant strictures can be inferred to amount to approximately 10% in patients with large duct PSC.[24] After extensive careful deliberations (outlined in the Supplementary Material), the panel delineated a number of criteria that coalesced into the working definition of a dominant stricture, as outlined in Box 2.

It must be mentioned that the biochemical criteria are based on limited studies and may be subject to change in the future.[25–27]

Dominant strictures in children virtually all occur in the teenage years when patients are adult- or nearly adult-sized, and so these definitions are deemed relevant to pediatric patients as well.

Of note, there is some discussion regarding the term *dominant* among experts of various professional societies. Some favor limiting the use of the word *dominant* to morphologic findings only at endoscopic retrograde cholangiopancreatography and adding the term *(clinically) relevant* to indicate functional impairment. In addition, when describing strictures on MRCP, only defined morphologic descriptors, such as *high grade* or *severe*, should be used rather than *dominant*; see Venkatesh et al.[28]

Pathology

Typical Primary Sclerosing Cholangitis

The pathologic changes occurring in PSC affect bile ducts of all sizes (intrahepatic and extrahepatic).[29] Classical fibrosing duct lesions mainly involve medium-sized (septal) bile ducts and are rarely (<20% of cases) seen in needle biopsy specimens, which sample small (interlobular) bile ducts. Similar changes also occur in diseases associated with secondary sclerosing cholangitis.[30–32] PSC cannot therefore usually be reliably distinguished from other chronic biliary diseases in liver biopsy samples. Features compatible with a diagnosis of PSC (and with other chronic biliary

Box 1. Consensus Statements

1. Clinical symptoms
   1.1. Assessment of symptoms in patients with PSC for clinical trial purposes should be performed through disease-specific and validated quantitative tools.
   1.2. Assessment of symptoms in patients with PSC should take into consideration and be distinguished from symptoms attributable to active inflammatory bowel disease and other coexistent conditions.

2. Laboratory markers
   2.1. The presence of significant elevations of serum aminotransferase activity (>5 × ULN) and/or IgG (>2 × ULN) can be indicative of features of coexisting autoimmune hepatitis and should trigger consideration of liver biopsy for diagnostic and stratification purposes when considering enrolling a subject in a clinical trial.
   2.2. Serum IgG4 concentrations can be elevated in patients with PSC, in the absence of classical features of IgG4-related disease, but IgG4 elevations are not validated markers of disease diagnosis, severity, prognosis, or treatment.

3. Imaging
   3.1. The pattern of PSC can be defined according to the appearances of cholangiography using high-quality magnetic resonance cholangiography (MRC) (at least 1.5 T):
      3.1.1. Small duct when a recent cholangiogram (not older than 1 year) is normal
      3.1.2. Intrahepatic when there are intrahepatic changes but the common ducts and first-order ducts are normal
      3.1.3. Extrahepatic disease when the common ducts and/or the first-order ducts are involved

4. Histology
   4.1. Histologic findings in a liver biopsy sample from patient suspected to have PSC can be defined (classified) as follows:
      4.1.1. Typical of PSC: features of fibrosing cholangiopathy present (periductal fibrosis, fibro-obliterative duct lesions)
      4.1.2. Compatible with PSC: features of chronic biliary disease present (see text for further details) without typical bile duct lesions
      4.1.3. Atypical for PSC: features atypical for PSC present. Examples include
         • unusually prominent inflammatory activity suggesting the possibility of PSC-AIH overlap syndrome
         • features suggesting an alternative diagnosis, such as fatty liver disease, or IgG4-associated cholangitis.
   4.2. A liver biopsy specimen showing typical or compatible histologic features is required to establish a diagnosis of small duct PSC.
   4.3. In a person with PSC, a liver biopsy specimen showing at least moderate interface hepatitis in addition to features compatible with or diagnostic of PSC is required to establish a diagnosis of PSC with features of AIH or PSC-AIH overlap syndrome.
   4.4. The histologic features that indicate disease progression (staging) in PSC include fibrosis, bile duct loss, and evidence of chronic cholestasis (demonstrated by deposition of copper-associated protein in periportal hepatocytes).

5. Concurrent IBD
   5.1. The definition and description of IBD in PSC should follow the European Crohn's and Colitis Organization (ECCO) guidelines and Montreal classification. Any patient with established PSC should undergo a full ileocolonoscopy with histology before concurrent IBD may be excluded.
   5.2. When assessing the existence of backwash ileitis, it is recommended that the ECCO definition be followed. This defines backwash ileitis as continuous extension of macroscopic or histologic inflammation from the cecum into the most distal ileum.

6. Staging
   6.1. Disease staging of PSC is defined as the histologic progression from initial disease onset to cirrhosis.
   6.2. A clinically significant change in disease stage is defined by a 1-point change in the Ludwig or Nakanuma system or a 2-point change in the Ishak system.
   6.3. Histologic cirrhosis is a clinically significant endpoint.
   6.4. Cirrhosis (stage 5–6 by Ishak) in PSC can be defined by an LS of >14.4 kPa measured by VCTE.
   6.5. Cirrhosis (stage 5–6 or greater by Ishak) in PSC can be defined by an ELF score of >9.8 or FibroTest of >7.3.

7. Clinical endpoints
   7.1. Liver transplant:
      Liver transplant is an appropriate endpoint in PSC clinical trials. However, divergent indications for transplant listing (end-stage disease, dysplasia, CCA, symptoms, intractable cholangitis) and method of transplantation (deceased vs living donation) should not be grouped into a single endpoint because of the wide heterogeneity of clinical practice.
   7.2. Liver-related death:
      Liver-related death in the setting of PSC is defined as death from clinically significant portal hypertension, synthetic liver dysfunction, or specific complications from biliary disease such as hepatobiliary infections.

8. Cancer development
   8.1. Cholangiocarcinoma:
      8.1.1. CCA in PSC requires pathologic confirmation and is classified according to CCA in general.
      8.1.2. Dysplastic changes considered precursors to CCA in PSC are defined by standard criteria.
   8.2. Colorectal carcinoma:
      8.2.1. CRC in the setting of PSC is defined according to standard criteria.

Box 1. Continued

9. Pediatric PSC
   - 9.1. Pediatric PSC is not a specific disease phenotype. PSC in children should be described in terms of small vs large duct involvement, whether features of overlap with AIH are present or absent, and whether IBD is present or absent, as in adult patients.
   - 9.2. Terms such as *juvenile sclerosing cholangitis* and *autoimmune sclerosing cholangitis* should be avoided.
   - 9.3. When gGT is substituted for ALP, the consensus definitions in this document are applicable to children.

10. Recurrent PSC
   - 10.1. The diagnosis of rPSC is based on the presence of compatible radiologic changes (using high-quality MR) with/or without histologic findings, along with the exclusion of other causes of similar findings.

Box 2. Working Definition of Dominant Stricture

A stricture is called a ***possible dominant stricture*** when it meets the following criteria before ERC:

- Imaging
  - High-quality MRCP or ERC with narrowing of any length in extrahepatic or first-order intrahepatic ducts, often—but not necessarily—with upstream dilatation

TOGETHER WITH

- Symptoms and biochemistry
  - Significant worsening of cholestatic symptoms within last 2 months:jaundice , biliary infection, pruritus, or RUQ pain
  - *and*
  - Bilirubin and/or ALP: absolute level of >1.2 × ULN and recent increase, for example, >1.2 × baseline[25]

OR

- Biochemistry alone
  - Bilirubin and/or ALP: increase within past 6 months, for example, >1.5 × baseline, or absolute level of >2 × ULN if no previous measurement within 6 months is available[26]

A dominant stricture can be called a ***definite dominant stricture*** when it meets the following criteria:

- The abovementioned imaging and biochemistry/symptom criteria before ERC

TOGETHER WITH

- Difficulty to pass with a standard 5F catheter during ERC

OR

- Symptomatic and/or biochemical response (eg, a >20% drop in ALP and/or total bilirubin) to treatment 2–4 weeks after dilatation/stenting

diseases such as PBC) include bile duct loss, ductular reaction, a biliary pattern of interface activity, and changes related to chronic cholestasis in periportal hepatocytes (cholate stasis)[29] (Box 1, CS4.1).

Small Duct Primary Sclerosing Cholangitis

Liver biopsy is generally considered to be essential for a diagnosis of small duct PSC[3,4,33] (Box 1, CS4.2). However, the histologic changes required to make this diagnosis have not been defined clearly or applied uniformly. In the largest study providing detailed histologic findings, only 4 of 25 (16%) cases had fibrosing duct lesions, with the remainder having features of chronic biliary disease compatible with PSC.[34]

Primary Sclerosing Cholangitis–Autoimmune Hepatitis Overlap Syndrome (Primary Sclerosing Cholangitis With Autoimmune Hepatitis–Like Features)

Liver biopsy is recommended for the diagnosis of PSC with AIH–like features, also called PSC-AIH overlap syndrome.[3,4,17,33,35] However, histologic criteria for the hepatitis features required to diagnose the AIH component of the syndrome are not clearly defined. It is worth noting that portal inflammation, including plasma cells, and interface hepatitis can occur as part of the normal spectrum of changes seen in PSC, and defining a point at which inflammatory changes are sufficient to suggest a diagnosis of overlap syndrome with AIH can thus be difficult. Current guidelines require the presence of at least moderate interface hepatitis to diagnose the PBC-AIH overlap syndrome, and it seems reasonable to use a similar approach in patients with PSC[4,17] (Box 1, CS 4.3) Of note, the panel prefers using the term *PSC with features of AIH* rather than *PSC-AIH overlap syndrome*, because most cases are probably better regarded as a variant of PSC in which there are unusually prominent inflammatory features that may resemble those seen in AIH.[17]

Diagnostic Criteria for Primary Sclerosing Cholangitis

The panel arrived at consensus regarding the diagnostic criteria for PSC outlined in Box 3.

Box 3. Diagnostic Criteria for PSC

Large duct PSC
- Required criterion:
  - Compatible[a] radiologic findings in a high-quality[b] MRCP/ERC
- Other criteria:
  - Elevated serum markers of cholestasis (ALP, gGT in children)
  - Concurrent clinical or histologic features of IBD
  - Histologic features compatible with PSC

A diagnosis of ***definite large duct PSC*** can be made when a patient has, in the absence of apparent causes of secondary sclerosing cholangitis (see *Supplementary Table 1*), the following:
- A high-quality MRCP/ERC with features compatible with sclerosing cholangitis

TOGETHER WITH
- At least 1 other criterion

A diagnosis of ***probable large duct PSC*** can be made in the absence of apparent causes of secondary sclerosing cholangitis (see *Supplementary Table 1*) when a patient has the following:
- Equivocal findings on MRCP/ERC

TOGETHER WITH
- at least 2 other criteria

OR
- compatible findings on high-quality MRCP/ERC but no additional criteria fulfilled

Small duct PSC
- Required criteria:
  - Recent (<1 year) normal high-quality ERC or MRCP
  - Histologic features typical of or compatible with PSC
- Other criteria
  - Concurrent overt or histologic features of IBD
  - Increased ALP (or gGT in case of pediatric cases)

In the absence of likely other cholestatic disorders (eg, drug-induced liver injury [DILI]; see *Supplementary Table 1*), a diagnosis of ***small duct PSC*** can be made when a patient has the following:
- A normal high-quality MRC/ERC

TOGETHER WITH EITHER
- Histologic features typical of PSC

OR
- Histologic features compatible with PSC

  TOGETHER WITH BOTH
  - Concurrent overt or histologic features of IBD
  - Increased ALP (or gGT in case of pediatric cases)

[a]*Compatible* here means characteristic bile duct changes with multifocal strictures and/or segmental dilatations in the intra- and/or extrahepatic biliary tree.
[b]A high-quality ERC requires adequate filling of the bile ducts up into the third-order intrahepatic bile ducts. A high-quality MRCP requires a magnet with a minimum field strength of 1.5 T after 4 hours of fasting with T2-weighted coronal 3-dimensional MRC imaging.[20,36]

Concurrent Inflammatory Bowel Disease

Primary sclerosing cholangitis and IBD are closely correlated. In a cohort of 7126 patients with PSC from 37 mainly tertiary referral centers throughout Europe, North America, and Australia, 70% developed IBD at some point.[5] Conversely, a small study from Singapore reported a prevalence of symptomatic IBD of 20%.[37] A nationwide survey in Japan showed that overt comorbid IBD is seen in 34% of patients with PSC.[38]

Interestingly, in a tertiary referral cohort of 184 patients with PSC from Oslo, all of whom underwent an ileocolonoscopy, Jorgensen et al[39] found at least histopathologic evidence of IBD in 84%, whereas endoscopic signs of IBD were present in only half of these. The vast majority of patients with PSC/IBD have UC, less than 20% have Crohn's disease, and in about 5% the bowel inflammation is classified as IBD unspecified. IBD precedes the diagnosis of PSC in approximately 60%, a concomitant diagnosis is made in up to 25% of patients, and PSC can precede IBD in about 15% of cases.[40]

The other way around, PSC among patients with IBD is rare. In a population-based cohort of 1291 Dutch patients with IBD, the prevalence of PSC was 1.7%.[41] Of note, in 2 recent studies applying screening MRCP in large

groups of patients with long-term IBD, abnormalities suggesting sclerosing cholangitis were found in 8.1%–14%, whereas only one third of those patients were previously known to have PSC.[42,43]

Distinctions From Regular Inflammatory Bowel Disease?

It is generally believed that the IBD phenotype associated with PSC is distinct from IBD without PSC and also behaves differently.[40,41,44] There is a clear tendency for right-sided colonic involvement, but the panel concluded that there is currently insufficient evidence to implicate backwash ileitis and rectal sparing as distinct features of PSC-associated colitis (Box 1, CSs 5.1 and 5.2). For a detailed discussion on PSC-associated IBD, see the Supplementary Material.

Staging

The purpose of disease staging is to determine prognosis and treatment response (Box 1, CS 6.1). Staging by a functional measure is not possible in early-stage PSC. Thus, staging refers to the measurement of fibrosis and may be measured directly or indirectly. PSC is also defined by bile duct function, and therefore staging systems incorporating bile duct loss and features of chronic cholestasis may be superior to those that measure only fibrosis.

Common staging systems, such as the METAVIR and Ishak scoring systems, have not been well studied in PSC. The Ludwig system has been most widely used,[45] whereas the Ishak and METAVIR systems have been studied in PSC in a limited fashion.[46–48] The Nakanuma system developed for PBC[31] incorporates bile duct loss and cholestasis and has been applied to PSC in 2 studies.[32,48]

A potential limitation of histologic staging in PSC relates to disease heterogeneity and the limited amount of liver sampled in a liver biopsy. However, of 56 paired biopsy specimens taken at the same time and interpreted by a single pathologist, Ludwig stage was in agreement in 73%; only 16% varied by 1 stage and 11% by 2 or more stages.[49] Inter- and intraobserver variability using the Ludwig, Ishak, and Nakanuma systems show good agreement ($\kappa = 0.62–0.67$).[48]

The progression of histologic stage over time has been studied in a single observational study and 15 clinical trials in which liver biopsy was included as an endpoint and is discussed in detail in the Supplementary Material.

Histologic stage has been found to be an independent predictor of transplant-free survival and liver-related events in several studies[10,48,50–52] (Box 1, CS 6.2). However, only Nakanuma staging was predictive of PSC-related death and liver transplantation.[48] Histologic progression to cirrhosis has traditionally been recognized by regulatory agencies as a surrogate endpoint. Because of the complexity of PSC, no progression to cirrhosis together with some other measure (eg, serum marker) may be acceptable as an appropriate coprimary endpoint by the US Food and Drug Administration[12] and European Medicines Agency[53] (Box 1, CS6.3).

Liver Stiffness Measurement

Noninvasive staging of liver disease by liver stiffness (LS) has gained popularity. However, LS in PSC may be affected by transient episodes of cholestasis. Studies in PSC are limited to vibration-controlled transient elastography (VCTE) and magnetic resonance elastography.[54–57]

LS measured by VCTE has been correlated with Ludwig,[56] METAVIR,[57] and Ishak stages.[58] Baseline LS and rate of change in LS are independent predictors of transplant-free survival and other liver-related outcomes[57,58] (Box 1, CS 6.4).

Serum Markers

Serum markers such as the enhanced liver fibrosis (ELF) test, Pro-C3, and lysyl oxidase L2 (LOX-L2) offer the potential to measure the balance of fibrosis formation and resorption, whereas the aspartate transaminase–platelet ratio index (APRI) and fibrosis-4 (FIB-4) reflect the consequences of advanced fibrosis and may not be helpful for early-stage disease. Ishak stage has been correlated moderately with ELF, APRI, and LOX-L2 and weakly with FIB-4.[59] For bridging fibrosis, the area under the receiver operator curves of ELF, FibroTest (Biopredictive, Houilles, France), APRI, and LOX-L2 were similar (0.72–0.77) and significantly higher than FIB-4 (0.62; $P < 0.03$ for all).

ELF and Pro-C3 have independently predicted clinical outcomes of death or liver transplantation and PSC-related events.[60–62] APRI was included in all 3 of these studies and in the VCTE study by Corpechot et al,[57] and in none of the studies was APRI found to be an independent predictor of clinical outcomes (Box 1, CS 6.5).

Clinical Endpoints

The design of clinical trials aimed at investigating therapeutic measures that improve the prognosis of PSC is complicated by the slow progression of the disease and low occurrence of clinically relevant endpoints, such as end-stage liver failure resulting in transplantation or death.[63] Therefore, there is an urgent need for surrogate endpoints that are reasonably likely to predict how a patient feels, functions, or survives.[12] For a detailed discussion on surrogate endpoints in PSC, the reader is referred to the recent IPSCSG position paper and US Food and Drug Administration guidance paper on this topic.[7,12] Here, the focus will lie on defining solid clinical endpoints, such as cirrhosis, liver transplantation, liver-related death, and bacterial cholangitis, that are relevant to the rational design of PSC clinical trials.

Cirrhosis

The diagnosis of cirrhosis in PSC may be performed by histologic sampling by biopsy or estimated by elastography (see the earlier discussion on staging). Furthermore, the development of decompensated cirrhosis (eg, ascites, hepatic encephalopathy, or variceal bleeding in a patient with cirrhosis) is a major clinical event and prognostic indicator associated with significant reduction in survival. One recently published prognostic scoring system, the PSC Risk Estimate Tool, focuses on hepatic decompensation and has a high predictive ability, with a C-statistic of 0.90.[64] Cirrhosis with decompensating events may therefore be an additionally meaningful clinical endpoint in PSC and should be further evaluated as such in subsequent studies.

Liver Transplant

Liver transplant is the only potentially curative modality for patients with PSC who progress to advanced cirrhosis and end-stage liver disease. Indeed, liver transplant–free survival is a commonly used clinical endpoint by which to assess the effect of therapeutic agents in many hepatic diseases, including cholangiopathies.[65] As such, it is a frequent clinical endpoint in PSC studies. More background on liver transplant as an endpoint is discussed in the Supplementary Material.

There is considerable heterogeneity in the clinical use and timing of liver transplantation for patients with PSC. Consequently, a liver transplantation event as a clinical endpoint in PSC trials must be defined with an additional level of clarity (Box 1, CS 7.1). Specifically, it should clearly detail the indication (decompensated cirrhosis, malignancy/dysplasia, refractory cholangitis, or quality of life), method of transplantation (deceased donor, living donor), and model of end-state liver disease at the time of transplant. Because the use of transplantation is not an acceptable indication for patients with dysplasia or quality of life in most countries, it may be appropriate to exclude such events.

Liver-Related Death

Liver-related death is a manifestation of progressive disease from biliary cirrhosis to end-stage liver disease with decompensated cirrhosis. In the context of PSC, liver-related death is typically caused by impaired liver function and complications of portal hypertension such as variceal bleeding, ascites, and hepatorenal syndrome. In addition, specific causes of liver-related death unique to PSC also include complications from large-duct strictures including refractory cholangitis and multiorgan sepsis stemming from biliary abscesses. Therefore, the definition of liver-related death as an endpoint in PSC should additionally include and specify these unique causes of death (Box 1, CS 7.2).

Bacterial Cholangitis

Patients with PSC frequently develop acute ascending bacterial cholangitis as a result of biliary obstruction or bile flow disruption from strictures. Indeed, in the recent clinical trial of simtuzumab for patients with PSC, acute cholangitis (13%) accounted for the vast majority of overall clinical events that occurred during the study and was common in both patients receiving the study drug and those receiving placebo.[47] Therefore, acute cholangitis has a major impact as a relevant clinical endpoint in both observational and therapeutic studies.

The panel was unable to reach consensus through the Delphi process on the definition of acute bacterial cholangitis in the context of PSC. This highlights an urgent, unmet need for dedicated studies comparing Tokyo, Wannhoff (see Supplementary Material), and other potential criteria so that a uniform approach can be used as a clinical endpoint in therapeutic trials.

Cancer Development

Cholangiocarcinoma and Gallbladder Carcinoma

Patients with PSC are predisposed to the development of hepatobiliary malignancies with standard incidence ratios of approximately 160.[66] The relative risk of CCA specifically is even higher. In a population-based study including 590 patients with PSC from the Netherlands, there was a 398-fold increased risk for developing CCA compared to the general population (standard incidence ratio, 398; 95% confidence interval, 246–608).[6] The frequency of CCA among patients with PSC varies among studies, generally ranging from approximately 7% in population-based series up to approximately 15% in patient cohorts from referral centers.[6,67,68] A high proportion (27%–50%) of CCA cases are diagnosed concomitantly with PSC or within the first year after diagnosis of PSC.[5,6] The risk of CCA persists throughout the PSC disease course, with an annual incidence rate of 0.5%–1.5%.[5,66] The condition carries a dismal prognosis and is a major cause of death in patients with PSC.[6,69]

CCA in PSC can arise along the entire biliary tree. Because there is no classification specific for PSC-associated CCA, classification follows that of CCA in general[70] (Box 1, CS 8.1.1). According to its anatomic location within the biliary tree, CCA in PSC thus is classified as intrahepatic (proximal to the secondary branches of the right and left hepatic ducts), perihilar (between the secondary branches of the right and left hepatic ducts and the common hepatic duct proximal to the cystic duct origin), and distal (tumors of the common bile duct, up to but not including the ampulla of Vater).

There are data strongly supporting a metaplasia–low-grade dysplasia–high-grade dysplasia sequence in PSC-associated CCA.[71] The contention that dysplasia is a precursor of and associated with PSC-CCA has provided the basis for the policy of assessing dysplastic changes in biliary brush specimens obtained during ERC. The specificity of biliary brush cytology in PSC is high, whereas sensitivity is low (pooled specificity and sensitivity in meta-analyses of 97%–99% and 43%–52%, respectively[72,73] (Box 1, CS 8.1.2).

Serum carbohydrate antigen 19-9 is usually elevated in PSC-CCA, but a normal value does not exclude CCA. Elevated serum carbohydrate antigen 19-9 levels may also be seen in PSC without biliary malignancy. Sensitivity and specificity of this biomarker depend on cutoff levels.

Patients with PSC are predisposed to gallbladder abnormalities, including gallstones, inflammation, and benign and malignant neoplasms. The frequency of gallbladder cancer is in the range of 0.6%–3.5% in the largest patient series. Gallbladder mass lesions or polyps harbor a cancer in approximately 60% of cases.[74]

Patients with PSC with cirrhotic-stage disease may also develop hepatocellular carcinoma, but the frequency is possibly lower than in cirrhosis from other causes.

Colorectal Cancer

Meta-analyses have concluded that there is a 3- to 4-fold increased risk of colorectal cancer (CRC) in patients

with PSC and UC compared to those who have UC without PSC.[75,76] Dysplasia in PSC-associated UC follows the accepted histopathologic criteria in IBD[77,78] (Box 1, CS 8.2.1). Overall, the reported 10-year cumulative risk of dysplasia or CRC in PSC-IBD varies between 0% and 14%.[44,79] CRCs in PSC-IBD are more often localized to the right colon as compared to observations in IBD without PSC.[80] CRC in patients with PSC is diagnosed at a younger age than in IBD only. An increased risk of CRC in Crohn's disease associated with PSC remains uncertain, and the risk in patients with PSC without IBD does not appear to be increased.[44] The risk of CRC in PSC-IBD persists and may be even higher after liver transplantation.[81]

Pediatric Primary Sclerosing Cholangitis

Children with PSC have fewer disease complications at presentation compared to adults. Dominant strictures, bacterial cholangitis, and cholangiocarcinoma are far less than in adults.[66,82–86] These differences appear to represent an earlier stage of the same disease present in adults, rather than being indicative of a unique phenotype of PSC. After 10 years of follow-up, patients with pediatric-onset PSC have rates of complications similar to adults in the second and third decades. The 10- to 15-year survival with native liver is similar in groups diagnosed in the teenage years vs in the 20s and 30s.[5,82] Current evidence does not support a distinct pediatric PSC phenotype. Any cutoff age (such as 18 years) to distinguish pediatric PSC as a distinct phenotype is arbitrary and has no pathophysiologic or epidemiologic basis (Box 1, CS 9.1).

Features of overlap with AIH are present in at least 33% of children[82,83] but only 7% of adults with PSC.[87,88] Formal diagnostic criteria for an AIH-PSC overlap syndrome and its treatment are lacking, and some of this difference may be sampling bias. Most children with PSC undergo liver biopsy regardless of biochemistry. The role of immunosuppression for various degrees or severities of subjectively interpreted overlap is unclear. Clinically, children labeled with features of AIH overlap have transplant-free survival analogous to patients with a classic large duct PSC phenotype.[82,83] Given the lack of standardized consensus diagnostic criteria for overlap in PSC, nonspecific and undefined terms such as *juvenile sclerosing cholangitis*, *autoimmune sclerosing cholangitis*, and *overlap syndrome* should be avoided (Box 1, CS 9.2). More research is needed to clarify this disorder and its treatment.

The cholestatic biochemical profile of pediatric PSC should include elevated gGT rather than ALP.

Normal values for ALP in children vary widely with age because of bone turnover and growth. ALP is thus not useful in following liver disease or in defining clinical events in children younger than 18 years. Age-specific norms may be 5 times those in adults during rapid growth in the teenage years. Liver-specific ALP isozymes are not routinely available or obtained in clinical practice. Because gGT is not affected by bone turnover and growth, and because ALP and gGT generally increase in parallel with one another, gGT is a better marker of cholestasis and biliary inflammation in children. It is reasonable to substitute gGT into adult-based definitions (eg, for dominant stricture) that otherwise rely on ALP (Box 1, CS 9.3).

Posttransplant Recurrence of Primary Sclerosing Cholangitis

After liver transplantation, patients with PSC may develop cholangiographic and histopathologic changes that resemble those of the original disease and that are suggested to represent PSC recurrence in the graft. Because several factors can contribute to bile duct strictures in the posttransplant setting and there are no specific features defining recurrent PSC (rPSC), the diagnosis is challenging[89] (Box 1, CS 10.1). Other potential causes of bile duct strictures (eg, hepatic artery thrombosis/stenosis, anastomotic strictures) should be excluded.

Histologic changes in rPSC include fibrous cholangitis with or without ductopenia, features of chronic cholestasis, and biliary fibrosis or cirrhosis. As with PSC in the native liver, fibrosing duct lesions mainly involve medium-sized (septal) bile ducts and are thus seen infrequently in liver allograft biopsy specimens obtained from patients with suspected rPSC. Instead, the diagnosis of rPSC is usually based on the presence of features supporting a diagnosis of chronic biliary disease compatible with PSC—these include features of cholate stasis, periportal deposits of copper/copper-binding protein, ductopenia, ductular reaction, and a biliary pattern of fibrosis. Similar histologic abnormalities also occur in cases of ischemic cholangiopathy, which cannot be reliably distinguished from rPSC in needle biopsy specimens. Patients receiving a transplant for PSC have an increased risk of developing chronic rejection, which may also be associated with ductopenia and, in some cases, with features of chronic cholestasis. In most cases, careful histologic examination, including review of preceding biopsies, and knowledge of relevant clinical events such as adequacy of immunosuppression, enables the distinguishing between rPSC and chronic rejection.[90]

Conclusions

Because the cause of PSC is enigmatic, its is course heterogeneous, and accurate diagnostic markers are lacking, both diagnosis and adequate classification for enrollment and stratification in clinical trials can be difficult. When there is a shortage of evidence-based data, a validated consensus processes among experts can offer a valuable alternative for formulating working definitions regarding the diagnosis and description of disease state and stage. Uniformity in defining disease parameters and endpoints is of great importance for research purposes such as the design of clinical trials, given the current lack of validated level 2 surrogate endpoints that are "reasonably likely to reflect how a person feels, functions or survives."[7,12] The results of this elaborate hybrid between a Delphi consensus and nominal group consensus process provide working definitions for most

Box 4. Next Steps

- Uniform application of working definitions in clinical trials and registries
- Focus on validation of surrogate endpoints of disease progression, such as noninvasive markers of fibrosis
- Validation of symptom-based tools
- Identifying a biomarker for early asymptomatic disease with normal liver enzymes

aspects of PSC, both with and without concurrent IBD as well as for the pediatric population. It should be noted that although the process of arriving at definitions was conducted rigorously, many of the definitions should be regarded as working definitions. These are subject to change when new data, for example, from clinical trials and large-scale prospective registries that are now under construction, become available. Some recommendations for next steps are summarized in Box 4.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.07.046.

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Conflicts of interest

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Supplementary Material

Methods

A consensus process was initiated applying a hybrid between a Delphi process and a nominal group process, as was previously used by the IPSCSG and the European Crohn's and Colitis Organization.[1,2] IPSCSG members were chosen on the panel based on their clinical expertise and transatlantic representation. The following topics were delineated: definition of PSC, dominant strictures, clinical presentation including phenotypes and symptoms, laboratory markers, imaging, pathology, concurrent IBD, staging, clinical endpoints, pediatric PSC, and rPSC. Topics were covered by individual panelists or in tandem who searched the available literature, on which concept definitions were circulated and rated anonymously through several Delphi rounds. All topics were covered by C.Y.P., D.A., K.M.B., C.L.B., M.D., D.T., and S.G.H. Participation and response rates were 100% for all Delphi rounds. For the topic on dominant strictures, additional panelists from both sides of the Atlantic were recruited (L.A., M.F., B.P., and C.R.). Subsequently, the consensus panel met in Washington, DC (October 2017), Paris (April 2018 and June 2018), and San Francisco (November 2018) for nominal group consensus meetings to discuss the results of all Delphi rounds. Definitions were discussed and reformulated until consensus was reached. This implied that agreement (including neutral) of at least 80% of voting panelists was required. Hence, only definition statements in the boxes are presented that meet this requirement. In case of disagreement, statements were discarded or an additional survey among IPSCSG members was performed using SurveyMonkey. Results from this survey were subsequently discussed. Additional Delphi consensus rounds were conducted in 2020, after which a consensus report was composed and approved by all panelists. Finally, the manuscript was submitted for review to the Steering Committee of the IPSCSG. Their comments were reworked through an additional Delphi consensus round and nominal group meeting, after which final endorsement was obtained from the Steering Committee.

Additional Background and Discussion

Laboratory Markers. *Primary Sclerosing Cholangitis and Normal Cholestatic Biochemical Parameters.* A French group performing systematic liver biopsy in patients with IBD undergoing surgery for their bowel disease observed normal liver biochemistry at the time of surgery in 22 of 29 (76%) of patients with histology compatible with PSC.[3] Belle et al[4] found PSC by MRC screening in 3.3% of 30 patients with IBD with normal liver test results. Recently, Culver et al[5] reported biliary abnormalities on MRC in 14% of 51 patients with extensive UC with normal liver biochemistry. Furthermore, 4 out of 19 (21%) patients with UC with colorectal dysplasia and normal liver test results had MRC morphology compatible with PSC. Conversely, in patients with pre-existing IBD and elevated liver enzymes in the study by Belle et al,[4] 49 of 203 (24%) patients had abnormal cholangiograms on MRC. In patients with pre-existing IBD, the identification of cholestatic serum liver biochemistry should trigger investigation for the diagnosis of PSC.

Distinction From IgG4-Sclerosing Cholangitis. PSC should be distinguished from a condition called IgG4-sclerosing cholangitis (IgG4-SC) or IgG4-associated cholangitis, which is the biliary manifestation of the multiorgan fibroinflammatory IgG4-related disease. This condition has an even stronger male predominance than PSC, and most patients are older than 60 years, but the cholangiographic abnormalities are often difficult to distinguish from PSC. Serum IgG4 subclass elevation is present in 80% of patients with IgG4-SC but can also be found in up to 25% of patients with PSC.[6] A serum IgG4 level of $>4 \times$ ULN was reported to offer positive and negative predictive values of 100% and 88%, respectively, to distinguish IgG4-SC from PSC.[7] In patients with a serum IgG4 of >1.4 and <2.8 g/L, the IgG4/IgG1 ratio, with a cutoff at 0.24, significantly improved both the positive predictive value and specificity for distinguishing IgG4-SC from PSC.[7] The IgG4/IgG1 ratio may be of utility in distinguishing PSC from IgG4-related cholangitis, but prospective validation in large cohorts is lacking.

Whether patients with PSC with an elevated serum IgG4 level have a more aggressive phenotype is uncertain. Some studies report a worse clinical outcome, whereas other larger studies show no impact on clinical outcome.[6] Data on immunosuppressive treatment are very limited. Two small series of patients with PSC with elevated serum IgG4 levels showed biochemical improvement upon treatment with oral corticosteroid treatment but no reversal of biliary strictures.[8,9]

Dominant Strictures. Stiehl et al in 2002 defined *dominant* as a stricture of 1.5 mm or less in the common bile duct or common hepatic duct or 1.0 mm or less in the right or left main hepatic ducts on cholangiography.[10] However, the measurement of stricture diameter depends on the filling pressure and volume of the injected contrast dye, so these criteria are rather fluid. Also, some patients can have very narrow strictures spanning almost the full length of the extrahepatic duct for years without complaints or increasing biochemical cholestasis. Therefore, the panel believed that the term *dominant stricture* should be reserved for those strictures that are biologically relevant. Because consensus was not uniform, an additional survey was conducted among 51 IPSCSG members (34 hepatologists, 9 gastroenterologists, and 7 expert endoscopists), among whom 17 (33%) performed ERC in patients with PSC themselves (Prof. Christian Rupp, personal communication, June 2020). Results of this survey showed that the working definition of a dominant stricture that received the most votes (20/51, 39.2%) was "an extrahepatic, hilar, or first-order intrahepatic duct stenosis, regardless of length or diameter, with new or worsening cholestatic serum liver tests and/or worsening cholestatic complaints such as pruritus, right upper quadrant pain, fever, fatigue."

Hence, a dominant stricture is a demonstrable stricture in the central bile ducts on imaging and is associated with functional consequences (biochemistry and/or symptoms). As such, a stricture in the common bile duct, common hepatic duct, or first-order intrahepatic bile ducts can be either nondominant, possibly dominant, or definitely dominant. To arrive at a workable communis opinio, an additional Delphi consensus was executed among 6 expert endoscopists with a vast track record of ERC in patients with PSC. This resulted in a working definition in which both cholangiographic and functional aspects were considered.

The 2- to 4-week interval after dilatation/stenting is used to accommodate the notion that in advanced liver disease, it may take >1 week to see improvement in bilirubin/ALP on the one hand, and highly inflammatory strictures tend to recur early, sometimes already after 4 weeks, on the other hand. Commonly, at 3 months, 60%–70% of patients will show a favorable response after therapy[11]; does this mean the other 30%–40% were not dominant strictures? This will be rather impossible to know, since some dominant strictures are refractory to dilatation therapy, and in other cases, they are not functionally relevant and the biochemical upsurge stems from intrahepatic worsening cholestasis. Hence, in the case of no or insufficient response, a stricture remains "possible" provided it was not already defined as definite by the criterion of difficulty to pass with a 5F catheter.

Concurrent Inflammatory Bowel Disease. *Disease Location.* The only systematic review on the phenotype of PSC-associated IBD reported a preponderance of involvement of the entire colon in 35%–95% of PSC/IBD cases.[12] The distribution between proctitis, left-sided colitis, and pancolitis in PSC/UC has been compared with UC without PSC in 3 studies. The prevalence values of pancolitis in PSC/UC in these studies applying the Montreal classification for disease distribution were 85%, 94%, and 95% compared to 45%, 62%, and 56% in the comparison groups, respectively ($P < 0.001$).[13–15]

In 1995, Loftus et al[16] reported a significantly increased prevalence of backwash ileitis in patients with PSC/IBD. Subsequent studies yielded conflicting results, likely because of the heterogeneity of patient selection and definition of backwash ileitis. Only the study by Boonstra et al allowed verification that the authors adhered to the definition of backwash ileitis as stated by the European Crohn's and Colitis Organization, for which continuity with colonic inflammation is a prerequisite.[2,13] In 3 other studies, the proportion of backwash ileitis was likely calculated relative to the total number of patients with UC instead of only those with at least right-sided colitis. Because pancolitis is much more prevalent among patients with PSC/UC as compared to UC control individuals, this may lead to an underestimation in the control group.[14–16] The available evidence does not allow us to implicate backwash ileitis as a particular feature of PSC/UC.

Rectal sparing is another feature that is considered to be more common in PSC-associated UC as compared to UC in general.[16,17] Diagnosis of true rectal sparing requires both endoscopic and histologic absence of inflammation with the exclusion of recent (<6 months) local steroid therapy.[12] Although there is a clear tendency that the colitis associated with PSC involves the proximal colon, there is currently insufficient evidence to regard rectal sparing as a distinct feature of PSC/UC.[12]

As for Crohn's disease, the proportion of isolated ileal involvement is much lower than in Crohn's disease in general.[12,13] Thus, involvement of the colon is the rule.

Disease Behavior. Several studies have indicated that PSC-associated IBD runs a relatively mild course.[13,18,19] However, these are only retrospective studies, which run a high risk of underestimation when assessing overall disease activity. Patients with colitis with concurrent PSC run a substantially increased risk of developing colonic dysplasia and cancer. See the section on cancer development.

Staging. *Histologic Staging.* In the only observational, longitudinal study, the rates of progression for those with stage II disease were 42%, 66%, and 93% after 1 year, 2 years, and 5 years, respectively.[20] However, in clinical trials over 1–5 years, 12%–37% of participants showed worsening of staging without a significant difference in mean stage from baseline[21–27] (see Supplementary Figure 1). In a 2-year placebo-controlled study of simtuzumab, mean hepatic collagen content did not change significantly over the course of 2 years, but 16% without cirrhosis at entry progressed to cirrhosis over 2 years.[28]

Clinical Endpoints. *Liver Transplant.* The use of liver transplantation as a clinical endpoint in the setting of PSC, however, presents several unique challenges. Although the development of decompensated cirrhosis, characterized by ascites, hepatic encephalopathy, variceal bleeding, or jaundice, in a patient with PSC is a clear sign of clinical deterioration, the timing of referral for transplantation varies widely across different countries. It also varies widely within countries such as the United States because of differing access to transplant and large regional variation in the supply of organs. Living donation is often considered an attractive alternative for patients with PSC and decompensated liver disease, and the model of end-stage liver disease at transplant is typically lower than for patients receiving deceased donor transplantation.[29] This often leads to earlier listing and transplantation at the select number of centers where living donation is routinely available. Furthermore, the degree to which patients with PSC are favored or disfavored by current allocation systems has been extensively debated around the world.[30,31] Transplantation for patients with CCA is a rapidly evolving discipline regarding eligibility and inclusion protocols but is not yet widely available for most patients at local transplant centers.[32] Finally, in some countries, transplantation is offered to patients with PSC who develop cholangiocellular dysplasia or to patients with intractable symptoms, whereas this is not practiced in many other countries.[33] Therefore, there is

considerable heterogeneity in the clinical use and timing of liver transplantation for patients with PSC.

Bacterial Cholangitis. There is no agreed-on definition of acute cholangitis in the setting of PSC, and therefore, its use in clinical trials is highly variable and unsatisfactory.

Establishing a clinical diagnosis of acute bacterial cholangitis, particularly in patients not requiring hospitalization, is challenging. The Charcot triad of fever, abdominal pain, and jaundice has been associated with acute cholangitis since the 19th century, although it is not sufficiently specific or rigorous to diagnose a clinical endpoint.[34] The most direct method for diagnosing acute bacterial cholangitis is retrieval of purulent discharge from the bile duct during ERCP. However, not all patients with PSC require or receive ERCP for the evaluation of suspected cholangitis, and furthermore, some patients with biliary purulence may not have other signs of acute infection such as fever and pain.[35] The Tokyo guidelines are the result of an international effort to systematize the diagnosis of acute bacterial cholangitis.[36–38] In this system, the following are measured:

(A) systemic inflammation, including fever of $>38^{\circ}$C and/or shaking chills or laboratory evidence of an inflammatory response (white blood cell count of <4 or $>10 \times 1000/\mu$L or C-reactive protein level of ≥ 10 mg/L);

(B) cholestasis including jaundice (bilirubin level of >2 mg/dL) or other abnormal liver test results (ALP, gGT, aspartate transaminase, or alanine aminotransferase level of $>1.5 \times$ ULN); and

(C) imaging including biliary dilatation or evidence of etiology on imaging (stricture, stone, stent).

A suspected diagnosis requires 1 item in A and 1 item in B or C; a definite diagnosis requires 1 item in A, B and C. Despite this more rigorous and objective assessment, the Tokyo system is of limited utility in the setting of PSC because many patients already have abnormal liver test results and imaging at baseline.

The recently published Wannhoff criteria for acute cholangitis, proposed as part of a dedicated study of patients with PSC, require either a single criterion (suppurative cholangitis on ERCP) or at least 1 major criterion (body temperature of $>38^{\circ}$C, leukocyte count of $>12 \times 1000/\mu$L, or C-reactive protein level of >75 mg/L) and at least 2 minor criteria (positive bile culture result, increase in ALP, or total bilirubin above $2 \times$ ULN, no other focus of infection).[39] This system does not require a change in imaging, which can be complex in the setting of PSC, and thus may be better suited to this disease. However, the Wannhoff system has not yet been studied in larger PSC populations and is currently not validated for use.

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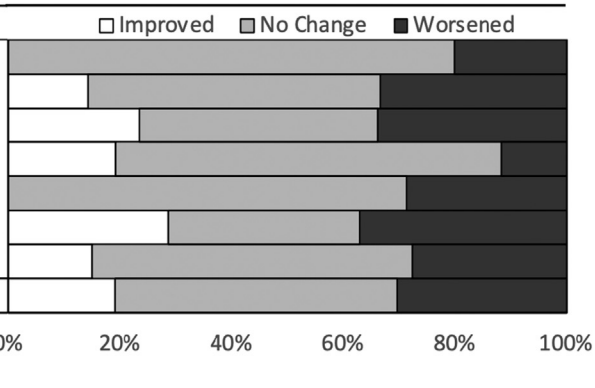
Study	Year	N	Duration (y)	System
LaRusso[1]	1988	70	2	Ludwig
Mitchell	2001	21	2	Ishak
Farkkila	2004	68	3	Ludwig
Cullen	2008	26	2	Ludwig
Hommes	2008	7	1	Ludwig
Muir	2016	216	2	Ishak
Angulo	1999	200	1[2]	Ludwig
TOTAL		608		



[1] Only histological worsening was reported.
[2] Median time between biopsies was 11 months.

Supplementary Figure 1. Progression of histologic stage over time.

Supplementary Table 1. Differential Diagnosis of PSC

Etiology	Main Examples
Inflammatory	IgG4-associated cholangitis Choledocholithiasis Secondary to bile duct surgery Follicular cholangitis Sarcoidosis Sclerosing cholangitis with granulocytic epithelial lesion Amyloidosis Graft-vs-host disease after bone marrow transplantation
Vascular	Ischemic cholangiopathy (eg, hepatic artery thrombosis, radiation injury, intra-arterial chemotherapy) Portal vein occlusion (portal biliopathy) Sclerosing cholangitis in critically ill patients
Infectious	AIDS-associated cholangiopathy Recurrent pyogenic cholangitis Cryptosporidium infection Liver fluke Ascariasis Septic shock
Neoplastic	Langerhans cell histiocytosis (histiocytosis X) Systemic mastocytosis Cholangiocarcinoma
Developmental/genetic	Bile transporter protein defects (eg, MDR3 deficiency) Ductal plate malformation/fibropolycystic liver disease Cystic fibrosis CD40 ligand deficiency (X-linked hyper-IgM syndrome)
Other/unknown	Drug-induced liver injury in the case of differentiation from small duct PSC Hypereosinophilia syndrome (?)