Epidemiology and Natural History of Primary Sclerosing Cholangitis

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Introduction

Primary sclerosing cholangitis (PSC) is a rare, heterogeneous, idiopathic, inflammatory disorder of the bile ducts resulting in strictures of the intrahepatic and/or extrahepatic bile ducts. The classic form of PSC, which accounts for the majority of PSC cases, as originally described has several characteristic features in addition to the classic cholangiographic features of strictures in the large and medium-sized bile ducts. The so-called large duct PSC occurs predominantly in men (male-to-female ratio, 3:2), is coexistent with IBD in 60–80 % of cases, and typically presents with cholestasis. The IBD typically is a pancolitis with frequent ileitis and rectal sparing. A small group of PSC patients present with clinical and histologic features compatible with PSC, except for the lack of typical cholangiographic findings and have been defined as small duct PSC [1]. IgG4-related sclerosing cholangitis, often found in association with autoimmune pancreatitis as one of many diseases associated with elevated IgG4 serum levels and tissue infiltration of IgG4 plasma cell, represents a separate disease entity and should be distinguished from PSC.

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Although the great majority of PSC patients have inflammatory bowel disease (IBD), only ~5 % of IBD patients will develop PSC, the underlying causes of this association remaining poorly understood. PSC affects all age groups and has been described in a variety of ethnic and racial groups but is best characterized in populations of Northern European descent. The natural history of PSC is variable in terms of liver disease progression with numerous possible clinical outcomes. In addition to progression to portal hypertension, cirrhosis, and its complications, PSC patients may also suffer from bacterial cholangitis, cholangiocarcinoma, gallbladder cancer, and colorectal adenocarcinoma. Increasing collaboration has led to an improved understanding of the epidemiology of PSC, the heterogeneity of its presentation, and its natural history.

Diagnosis

According to the American Association for the Study of Liver Disease (AASLD) practice guidelines, the diagnosis PSC can be made in "patients with a cholestatic biochemical profile, when cholangiography (e.g., magnetic resonance cholangiography [MRC], endoscopic retrograde cholangiography [ERC], percutaneous transhepatic cholangiography) shows characteristic bile duct changes with multifocal strictures and segmental dilatations, and secondary causes of sclerosing cholangitis have been excluded" [2].

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The AASLD guidelines also consider patients with clinical, biochemical, and histological features compatible with PSC but have a normal cholangiogram, to be classified as small duct PSC. However, these criteria are problematic for number of reasons.

First, not all patients with PSC demonstrate cholestatic liver test yet otherwise fulfill these criteria. Second, interpretation of cholangiograms can be difficult to quantify and limited by technical and interobserver variability. Although MRCP remains the initial diagnostic imaging tool of choice with a sensitivity 86 % and specificity 94 % of for the diagnosis of PSC [3, 4], a negative MRCP does not obviate the need for ERCP as MRCP lacks sensitivity in early PSC and can lack specificity in cirrhosis [5]. Third, the classic "onion-skinning" of concentric fibrosis is found in only a minority of PSC cases and is not specific to PSC. Finally, excluding secondary causes of sclerosing cholangitis can be difficult, particularly in patients without IBD who may have undergone cholecystectomy during an evaluation of cholestasis. In light of these limitations, there has yet to be a set of objective criteria upon which a case definition can be established. In fact, the defining features of the PSC cholangiogram may represent numerous different pathways leading to the same clinical disease. As we better understand the various clinical phenotypes, immunologic abnormalities, and genetic basis of PSC, the development of a more rigorous diagnostic framework may arise.

Signs and Symptoms

The typical symptoms of PSC include right upper quadrant abdominal discomfort and fatigue. Pruritus can occur but is typically episodic, coinciding with biliary obstruction. Signs and symptoms of bacterial cholangitis, including fever and right upper quadrant pain with or without jaundice, may also occur sporadically. Weight loss may also be reported at presentation. Although the majority patients have a concomitant IBD, it is frequently quiescent. Therefore, a colonoscopy is mandatory at PSC diagnosis in all patients. This should also include intubation of the terminal ileum to rule out ileitis.

Diagnostic Evaluation

As noted above, the diagnosis of PSC is typically entertained in the setting of cholestatic biochemical abnormalities. However, the diagnosis should also be considered in the setting of advanced liver disease of unknown etiology, particularly in individuals with IBD. Although no serologic markers have sufficient accuracy in diagnosing PSC, they are helpful in establishing the certainty in difficult cases. Serum IgG levels are elevated 1.5 times the upper limit of normal in approximately 60 % of PSC patients, and IgG4 levels can be found to be elevated in approximately 10 % of patients. The latter is of particular importance along with imaging and histology in order to exclude the diagnosis of IgG4-sclerosing cholangitis. In addition, a number of autoantibodies can be found with high prevalence. Notably, the atypical perinuclear antineutrophil cytoplasmic antibody (pANCA) is present in up to 80 % PSC patients but is also commonly found in patient with autoimmune hepatitis. Antinuclear antibody and anti-smooth muscle antibody are also frequently present, but alone should not be considered diagnostic of overlap with autoimmune hepatitis. The importance of liver biopsy and the diagnostic evaluation of PSC have decreased over time. Given that this is a disease of the medium and large-sized bile ducts that may be regionally affected, liver biopsy frequently does not reflect the disease or its severity. Nevertheless, liver biopsy remains an important diagnostic tool when there is a disproportionate elevation of serum aminotransferase levels to rule out overlap with autoimmune hepatitis or when the cholangiogram is normal and small duct PSC is suspected.

Epidemiology

The incidence and prevalence of PSC appears to be highest in North America and Northern Europe where it has been most extensively studied, and

estimates of approximately incidence and prevalence rates of 1–1.5 cases per 100,000 person-years and 6–16 cases per 100,000 inhabitants, respectively, have been reported [6–8]. However, there are several limitations to our understanding of PSC epidemiology, and current data may underestimate the true prevalence of PSC. Notably, prior to the widespread use of MR cholangiography, diagnosis relied upon liver biopsy or invasive cholangiographic methods such as endoscopic retrograde cholangiography (ERC) to diagnose PSC. For a disease with no proven therapy, many clinicians may have decided not to pursue the diagnosis of PSC in patients with IBD and abnormal liver tests. In addition, liver biochemistries may not be particularly sensitive to identify PSC among IBD patients. Without routine imaging of the biliary tree, the true prevalence of PSC cannot be known. Lack of awareness of PSC may lead to underdiagnosis as well. PSC is a rare disease and not well appreciated by general practitioners who may not entertain the diagnosis.

In addition to underdiagnosis, other structural limitations have prevented an accurate estimate of PSC prevalence and incidence. Specifically, most studies derive data from limited populations from specialized centers in specific geographic areas and are not truly population based. In addition, the lack of an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) code defining PSC has hampered true population-based estimates of PSC from administrative data. ICD-10 does little to rectify this issue but there is movement to change this for ICD-11.

Prevalence and Incidence Rates

Early studies of cohorts estimated that the incidence of PSC in North America and Northern Europe was approximately 0.9–1.3 cases per 100,000 person-years (Table 1.1) [6, 9, 10]. Subsequent population-based studies have estimated similar incidence rates [8, 11], while several other studies have placed the estimates at approximately 0.4–0.5 cases per 100,000 [12–14]. Importantly, two of these studies have demonstrated increasing incidence over time suggesting either an increasing incidence of disease or increasing rate of detection [8, 12].

Data on the prevalence of PSC in other parts of the world are limited. From questionnaire data from Spain and Japan, the estimated prevalence rates were 0.22 and 0.95 cases per 1000,000 inhabitants, respectively [15, 16]. PSC appears to be rare in native Alaskans [17], but PSC dispro-

Table 1.1 Estimates of incidence and prevalence of primary sclerosing cholangitis

Region	Study period	Number of cases	Incidence[a]	Prevalence[b]	Reference
Northern Europe					
Norway	1986–1995	17	1.3	8.5	[9]
Sweden	1992–2005	199	1.22	16.2	[8]
Netherlands	2000–2007	519	0.5	6.0	[12]
UK	1984–2003	46	0.91	12.7	[10]
UK	1987–2002	149	0.41	3.85	[13]
North America					
Rochester, MN	1976–2000	22	0.9	13.6	[6]
California	2000–2006	169	0.41	4.15	[14]
Calgary, Canada	2000–2005	49	0.92	NA	[11]
Spain	1984–1988	43	0.07	0.22	[15]
Japan	2007	415	NA	0.95	[16]

NA not available
[a]Per 100,000 person-years
[b]Per 100,000 inhabitants

portionately accounts for African-Americans listed for liver transplantation suggesting that they have a prevalence similar to whites [18].

Demographics

The demographic characteristics of patients with PSC have been similar regardless of the cohort being described. PSC disproportionately affects men with approximately two-thirds of patients with PSC being male. The age of diagnosis of PSC ranges from children to the elderly, but the median age of diagnosis is typically in the fourth decade [6–8, 12]. Notably, the peak incidence in men is younger than women. Approximately 10 % of cases are in children. The association between PSC and IBD has been consistently reported; however, earlier data suggested that approximately 80 % of patients with PSC had concomitant IBD. In contrast, more recent data estimate this value to be in the range of 65–70 %, with women having a lower prevalence of IBD compared to men with PSC [6–8, 12]. Across all series, nearly 80 % of PSC patients with IBD have ulcerative colitis, while fewer than 20 % have Crohn's disease [6–8, 12].

Natural History

Understanding the natural history of PSC is complicated by a multitude of challenges, most notably an unknowable onset of disease (Fig. 1.1). There is likely to be a preclinical period between the onset of disease and the abnormal cholangiographic findings, which represent established fibrosis. In addition, delay in diagnosis is common resulting in an artificially shortened time from diagnosis to clinical outcome. Further, there are several clinically important outcomes, such as cholangiocarcinoma and colorectal cancer, which are unrelated to liver disease severity. Finally, as with the epidemiology of PSC, changes in technology and increased awareness of the disease have likely lead to the diagnosis of less severe cases. Overall, this might lead to the erroneous conclusion that PSC is becoming more common but less severe.

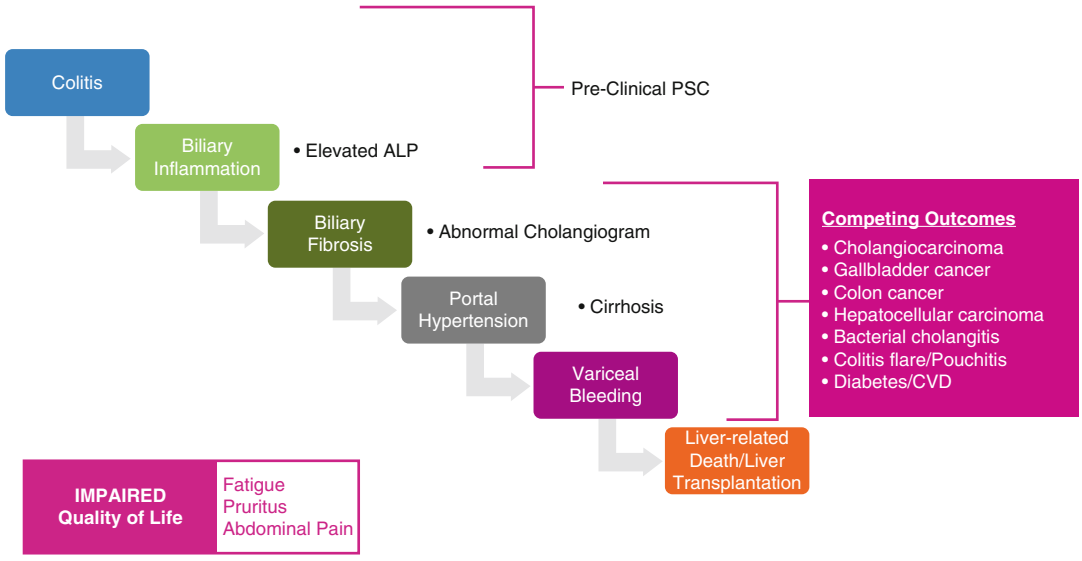

Fig. 1.1 The natural history of primary sclerosing cholangitis (PSC). Prior to the diagnosis of PSC, there is a preclinical stage, which likely involves colitis leading to biliary inflammation. Not until biliary fibrosis is present can the diagnosis of PSC be made by an abnormal cholangiogram. Subsequently, there is a progression of biliary fibrosis leading to portal hypertension, cirrhosis, and its complications. In addition, there are competing risk unrelated to the progression of the liver fibrosis

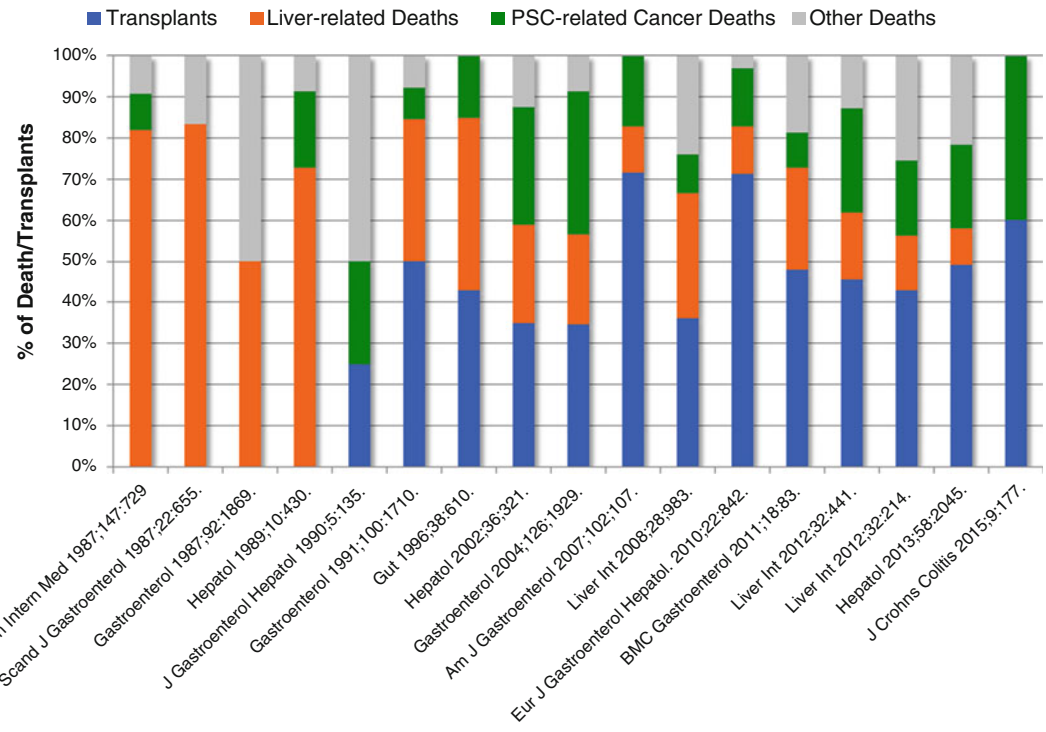

Fig. 1.2 Distribution of outcomes of death and liver transplantation among patients with PSC. In early studies, the majority of deaths were related to liver failure. Increasingly, the primary outcome has become liver transplantation with a smaller percentage dying from liver failure. A variable, but minor, percentage developed PSC-related cancers or die from unrelated causes [12, 19, 48–55]

Most commonly, PSC progresses similar to other chronic liver diseases with liver fibrosis leading to portal hypertension and its associated complications. In early studies, liver-related deaths accounted for approximately 70–80 % of mortality (Fig. 1.2). More recent studies suggest little change with clinical end points of liver transplantation and liver-related deaths still accounting for similar proportion of outcomes. Cancers related to PSC, including cholangiocarcinoma, gallbladder cancer, and colorectal cancer, make up 10–20 % of death in PSC. Like other biliary forms of liver disease, portal hypertension tends to be presinusoidal with esophageal varices developing early in the course of disease. In addition to cirrhosis, biliary strictures can lead to bacterial cholangitis and jaundice. Risks of malignancy are also increased. This includes not only a risk of cholangiocarcinoma and gallbladder cancer but also an increased risk of colorectal cancer in those patients with concomitant IBD.

The estimated median time from diagnosis of PSC to either death or liver transplantation based upon early studies ranged from 9 to 18 years (Fig. 1.3) [19–21]. However, these studies were from tertiary care and liver transplant centers with the potential for significant referral bias. This was illustrated by a study of all PSC patients treated at 44 hospitals in a large geographically defined area in the Netherlands comprising over 8 million people. In this population-based study, the estimated median survival from diagnosis of PSC until liver transplantation or PSC-related death was 21.3 years in the entire cohort compared to only 13.2 years for patients receiving care at a transplant center [12].

Risk Prediction in PSC

Predicting outcomes from PSC is important not only for individual patients but also for clinical

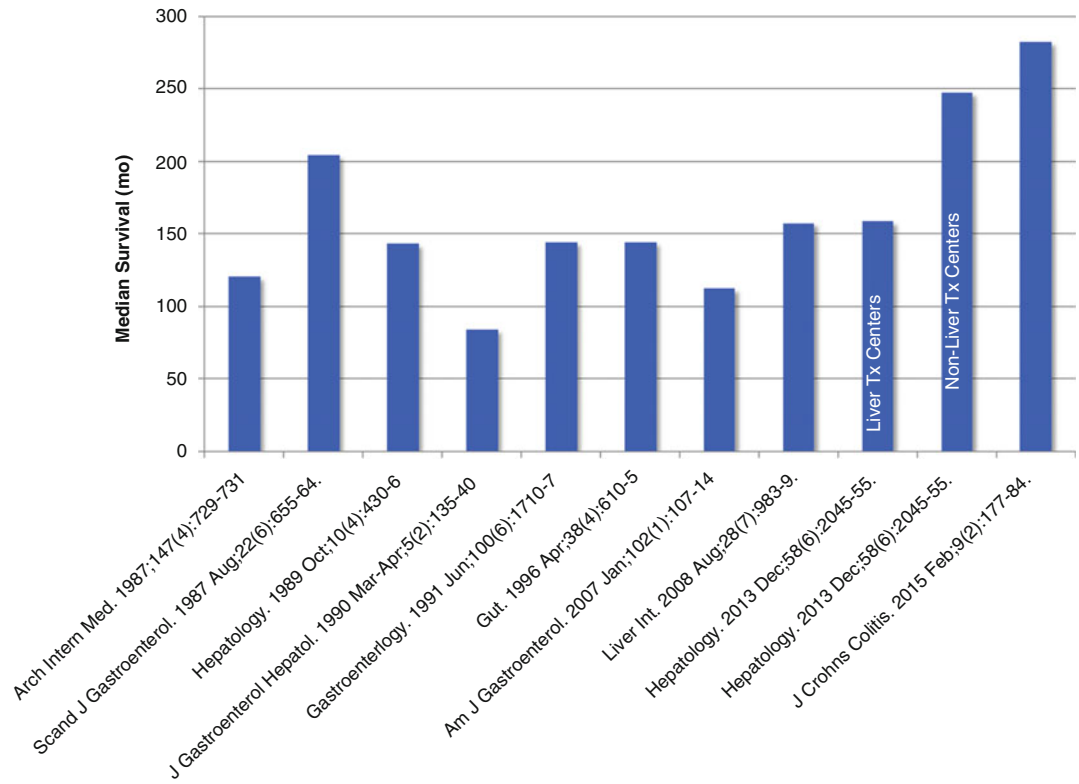

Fig. 1.3 The median transplant-free survival across multiple studies [12, 19, 48–55]

trial design and decisions on liver transplantation. Although the model of end-stage liver disease (MELD) score is used universally for predicting outcomes in patients with cirrhosis regardless of etiology, it is worth noting that the MELD score has not been studied in PSC patients with cirrhosis. Because cholestasis occurs relatively early in PSC compared to hepatocellular-based causes of cirrhosis, commonly used models for cirrhosis such as the Child-Turcotte-Pugh (CTP) classification and the MELD score may not adequately predict outcomes in PSC. In contrast, several risk models have been developed over time to prognosticate and predict outcomes in patients with PSC regardless of cirrhosis status. These models have incorporated different combinations of clinical, histological, and/or laboratory parameters (Table 1.2). As expected, bilirubin and markers of portal hypertension are common to all of the PSC models described. However, it is quite informative that only one model carried alkaline phosphatase into the final predictive model given recent findings that suggest normalization of alkaline phosphatase portends good long-term transplant-free survival.

The Mayo risk score, which unlike some other models, does not include histological criteria requiring a liver biopsy, is the only validated model, and remains the most commonly used [22]. It was developed and validated to prognosticate outcomes in patients with all stages of disease and is based purely on objective clinical and laboratory criteria. The revised Mayo risk score includes serum bilirubin, albumin, aspartate aminotransferase, age, and history of variceal bleeding. In derivation and validation cohorts, this score estimated survival up to 4 years after calculation [23].

Limitation of the Mayo risk score and other models include the lack of long-term predictions of outcome and lack of responsiveness to intervention making them less attractive as end points

Table 1.2 Prognostic models of survival in primary sclerosing cholangitis [19, 23, 52, 53, 56]

	King's ($n=126$)	Hannover ($n=273$)	Sweden[a] ($n=305$)	Europe[b] ($n=330$)	Revised Mayo ($n=405;124$)
Demographics					
Age	⊗	⊗	⊗	⊗	⊗
Laboratory/pathology					
Alkaline phosphatase	⊗				
Aspartate aminotransferase (AST)					⊗
Total bilirubin		⊗[c]	⊗	⊗	⊗
Albumin		⊗		⊗	⊗
Biopsy stage	⊗		⊗		
Clinical findings					
Hepatomegaly	⊗	⊗			
Splenomegaly	⊗	⊗			
Clinical events					
Variceal bleeding					⊗

[a]Cases with variceal bleeding (4 % of total) excluded
[b]Time-dependent model
[c]Persistently elevated bilirubin

in clinical trials. Noninvasive fibrosis markers, including measures of liver stiffness by transient elastography and serum markers of fibrosis, are currently being evaluated. In a prospective study of patients with PSC, liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE) was accurate at differentiating PSC patients into those with minimal to no fibrosis versus those with severe fibrosis and cirrhosis [24]. VCTE was superior to other noninvasive markers of fibrosis in patients with PSC, notably the FIB-4 score and the Mayo risk score. Furthermore, among 142 patients monitored with VCTE for an average of 3.9 ± 2.1 years, LSM demonstrated a slow progression in those patients with minimal fibrosis (F0 or F1) but an exponential increase in stiffness over time once patients reached a fibrosis stage of F2 or greater. Once patients reached an F4 stage of fibrosis (cirrhosis), the median time from compensated to decompensated cirrhosis was 3.6 years, with a significantly increased risk of liver-related complications in patients with either a greater amount of baseline fibrosis or a more rapid increase in their LSM [24].

The Enhanced Liver Fibrosis (ELF) score combines three serum markers: tissue inhibitor of metalloproteinases-1 (TIMP-1), hyaluronic acid (HA), and intact N-terminal propeptide of type III procollagen (PIIINP) and has also been studied in PSC patients [25]. Importantly, the ELF score was significantly great in PSC compared to ulcerative colitis patients without PSC, and ulcerative colitis disease activity did not appear to affect the ELF score. However, the ELF score did distinguish between mild and severe PSC disease defined by clinical outcome of transplantation or death with an area under the receiver-operator curve (AUROC) of 0.81. Additionally, in multivariable survival models, the ELF score was significantly associated with transplant-free survival, independent from the Mayo risk score. The ELF risk score correlated with VCTE in separate assessments, which highlights the applicability of either of these noninvasive measures of fibrosis as a means to prognosticate outcomes of patients with PSC [25].

Clinical Phenotypes

In addition to risk models and noninvasive markers, a variety of clinical features have been associated with differences in natural history and clinical outcomes. The classic form of PSC, which accounts for the majority of PSC cases, as

originally described has several characteristic features in addition to the classic cholangiographic features of strictures in the large and medium-sized bile ducts. Namely, large duct PSC occurs predominantly in men (male-to-female ratio, 3:2), is coexistent with IBD in 60–80 % of cases, and typically presents with cholestasis. The IBD typically is a pancolitis with frequent ileitis and rectal sparing. In addition, the IBD is commonly mild and asymptomatic. The association between PSC and IBD appears to be greater in Northern latitudes, although, even there, the frequency of non-IBD PSC is increasing.

Dominant bile duct strictures, defined as strictures with a diameter of less than 1.5 mm of the common bile duct or less than 1.0 mm of a hepatic duct within 2 cm of the bifurcation, develop in approximately half of PSC patients and are associated with poor outcomes even with endoscopic management [26, 27]. This decreased survival has been suggested to be due to the increased prevalence of cholangiocarcinoma. In contrast, small duct PSC, which comprises approximately 10 % of PSC cases, rarely progresses to large duct PSC and has a favorable outcome [1].

The impact of IBD, both in terms of its absence or type, on the natural history of PSC has increasingly been recognized. PSC in the absence of IBD tends to be equally distributed among men and women, is diagnosed at an older age [28], and may have a better prognosis [29]. The presence of Crohn's disease has also been associated with a better prognosis in recent studies [30, 31]. However, differentiating between ulcerative colitis and Crohn's disease is often difficult given that fistulizing or fibrostenotic Crohn's disease is rare in PSC. Studies of PSC in non-Caucasians are limited, but African-Americans listed for liver transplantation with PSC are younger and with greater MELD scores compared to whites with PSC [18].

Overlap between PSC and autoimmune hepatitis remains a controversial issue, especially regarding diagnostic criteria. The prevalence of this overlap has been reported to be between 1 and 53.8 % reflecting the lack of agreed-upon criteria. Case reports and clinical experience suggest two types of presentation. One in which there is coexisting features of both diseases; the other in which a typical case of autoimmune hepatitis transforms into a cholestatic variant. Interestingly, 10 % or more of patients with autoimmune hepatitis will have cholangiographic features consistent with PSC [32, 33]. Overlap with autoimmune hepatitis also appears to be more frequent in pediatric cases of PSC as discussed in Chaps. 4 and 6.

Recently, the rate of inflammatory bowel disease among African-Americans has been increasing with distinct clinical and genetic features. Not surprisingly, PSC has also been demonstrated to be prevalent in African-Americans. Genetically, there is still a strong HLA association with HLA-B8. In addition, among African-Americans listed for liver transplantation with the diagnosis of PSC, the male predominance is less pronounced, the frequency of the inflammatory valve disease is less, but the patients are listed at a younger age and with a greater MELD score suggesting a more aggressive disease [14, 18].

In addition to demographic and clinical features, laboratory markers may have prognostic value in distinguishing patients with PSC into groups with elevated IgG4 and normal serum alkaline phosphatase. Contrasting results on the impact of elevated serum IgG4 and disease course have been reported with the first study suggesting that an elevated IgG4 levels was associated with a shorter time from disease presentation to liver transplantation, while a second report was unable to replicate this finding[34, 35]. More consistent has been the finding that reduction and/or normalization in serum alkaline phosphatase levels is associated with longer survival times, irrespective of treatment leading to this normalization [36–39].

Complications

Malignancy in PSC

Patients with PSC are not only at risk for progressive liver fibrosis and liver failure but also are at significantly increased risks of three cancers:

cholangiocarcinoma, colorectal adenocarcinoma, and gallbladder carcinoma. Importantly, unlike the risk of hepatocellular carcinoma in chronic viral hepatitis, the risks of these cancers in PSC are not related to disease stage. In fact, aside from a greater incidence of cholangiocarcinoma in the first year following diagnosis, the annual incidence rates of these cancers appear to be constant. Details regarding hepatobiliary and colorectal malignancies are addressed in Chaps. 2 and 3, respectively.

Nonmalignant Outcomes of PSC

In addition to the progression to end-stage liver disease and malignant complications, there are several important nonmalignant outcomes related to PSC. These include the development of the dominant stricture, which as noted above is associated with a lower rate of survival, bacterial cholangitis, and hepatic osteodystrophy.

Dominant Stricture

Dominant strictures occur with a cumulative frequency of 36 to 57 % of patients with PSC. The presence of a dominant stricture is of particular concern for cholangiocarcinoma and should be evaluated by brush cytology and/or biopsy [45]. In the short term, management of dominant structures involves endoscopic evaluation and treatment. However, whether there is benefit to regular dilation in the absence of symptoms or worsening cholestasis has not been adequately studied.

Bacterial Cholangitis

The prevalence, incidence, and natural history a bacterial cholangitis and PSC have been rarely studied, primarily because the diagnosis is a clinical one. Patients with PSC frequently have abdominal pain and often report transient episodes of fever, which may resolve spontaneously. Among patients with PSC listed for liver transplantation, 48 % were reported to have developed bacterial cholangitis while awaiting transplantation [46]. Interestingly, there was no increase in wait-list removal for death or deterioration associated with bacterial cholangitis.

Hepatic Osteodystrophy

Osteopenic bone disease is frequent in patients with cirrhosis from any cause and has been well studied in patients with primary biliary cholangitis (PBC). Although PSC affects primarily younger men who are at very low risk of low bone mineral density, approximately 15 % of PSC patients have osteoporosis defined by a T-score less than −2.5 [47]. The presence of age ≥54 years or older, body mass index ≤24 kg/m^2, and inflammatory bowel disease for ≥19 years all correlated with osteoporosis.

Conclusion

PSC is a rare inflammatory disease of the bile ducts that is often associated with inflammatory bowel. It is unique among autoinflammatory diseases in its strong male predominance. The disease frequently progresses over decades to biliary cirrhosis and liver failure but may also result in malignancies of the bile ducts, gallbladder, and colon. These latter outcomes that are unrelated to disease stage make the development of prognostic models and surrogate markers problematic. In addition, the rarity of PSC and its heterogeneity requires international collaboration and cooperation to fully understand and classify the subphenotypes, which may lead to a better understanding of the underlying pathophysiology as well as more accurate predictive models.

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