Structured Literature Review of Evidence on the Clinical, Humanistic and Economic Burden of Primary Sclerosing Cholangitis (PSC)

EPH110

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Introduction

- Primary sclerosing cholangitis (PSC) is a chronic and progressive cholestatic liver disorder of unknown etiology often leading to cholestasis and liver failure[1]
- In the absence of curative treatment for PSC, the condition is managed with medications aiming to control symptoms and progression, with endoscopic retrograde cholangiopancreatography (ERCP) being used frequently for cancer surveillance and treatment of dominant strictures[1]

Objective

- To perform a structured literature review on PSC from peer-reviewed sources and gray literature, with a focus on epidemiology, natural history and disease progression, health-related quality of life (HRQoL), patient-reported outcomes (PROs), treatments and diagnosis, and clinical and economic burdens

Methods

- Literature databases (PubMed, Embase, Cochrane, the NHS Economic Evaluation Database and the Health Economics Research Centre database) were searched, limited to English-language publications from January 2015 to September 2022. Proceedings from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, Digestive Disease Week, the European Conference on Rare Diseases and Orphan Products and the American Conference on Advanced Treatments in Rare Diseases were also searched to supplement results
- Findings were screened by one reviewer by title and abstract. Potentially relevant articles were then screened as full text
- Inclusion and exclusion criteria of the structured literature review are summarized in **Table 1**

Table 1. PICOS predefined inclusion and exclusion criteria of the structured literature review

Domains	Inclusion criteria		Exclusion criteria
Population	• Patients with PSC, with or without comorbidities (i.e. classic PSC, large duct) • All demographics • All fibrosis stages		• Studies reporting data not on PSC • AIH overlap syndrome, small duct, IgG4 elevation
Intervention	No restrictions by intervention		
Comparator	No restrictions by comparator		
Outcomes	**Epidemiology** • Prevalence (n, %), annual • Incidence (n, %), annual • Prevalence of comorbidities (e.g. UC, Crohn's disease) **Diagnosis and treatment** • Methods of diagnosis • Treatment patterns in clinical practice **Disease progression** • Asymptomatic vs symptomatic • Cholestasis (i.e. ALP, GGT, bilirubin) • Hepatobiliary cancer (e.g. cholangiocarcinoma, HCC) • CRC • Fibrosis stages F0–F3 • Cirrhosis/decompensated cirrhosis • Liver transplant	**Burden of disease** • All-cause mortality vs liver-related mortality • Disability associated with symptoms, including: – fatigue – pruritus – abdominal pain **HRQoL and PROs** • Utility data • PRO measures/tools **Economic burden** • Direct and indirect costs associated with PSC • Healthcare resource utilization	Studies reporting outcomes other than those listed in the inclusion criteria
Study design	• Epidemiology studies • RCTs • Longitudinal studies • Real-world studies, which may include: – observational studies (prospective or retrospective) – registries – medical records/chart reviews	• Treatment/practice guidelines • Economic models • Systematic literature reviews or meta-analyses of the above studies/data	Opinion pieces, editorials, commentaries, letters to the editor
Language	English		Non-English

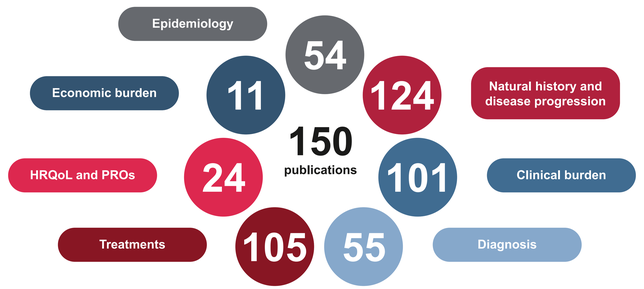
AIH, autoimmune hepatitis; ALP, alkaline phosphatase; CRC, colorectal cancer; GGT, γ-glutamyl transferase; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; IgG4, immunoglobulin G4; PICOS, population/intervention/comparison/outcome/study design; PRO, patient-reported outcome; PSC, primary sclerosing cholangitis; RCT, randomized controlled trial; UC, ulcerative colitis.

Results

Search outcomes

- The searches identified 5,475 unique publications, of which 150 were included (**Figure 1**)

Figure 1. Summary of findings from the structured literature review per topic



Individual numbers do not add to 150 as several publications covered multiple topics.

HRQoL, health-related quality of life; PRO, patient-reported outcome.

Epidemiology of PSC

- PSC is a rare disease, but incidence has increased over time: US data (Olmsted County, MN) showed that PSC incidence nearly doubled from 0.79 per 100,000 person-years in 1976–2000 to 1.47 per 100,000 person-years in 2001–2017 (age- and sex-adjusted)[2]
- It is more common in men and adults: median age at diagnosis ranges from 31 to 58 years[2–24]
- PSC is strongly associated with inflammatory bowel disease (IBD), which is reported in 37–88% of patients with PSC.[2–4,7,10,11,14,15,18,22,23,25–27] Ulcerative colitis (UC) is the most prevalent IBD in patients with PSC, ranging from 43% to 87% of all concomitant IBD cases in all but two studies (which reported UC in 33.2% and 5.33% of cases)[4,7,9,11–13,15–17,25–31]
- The most frequent non-IBD autoimmune diseases diagnosed in patients with PSC include autoimmune thyroiditis (42.1%), autoimmune hepatitis (13.2%), rheumatoid arthritis (7.9%), autoimmune pancreatitis (5.3%) and sarcoidosis (5.3%)[14]
- Other comorbid conditions observed with PSC are autoimmune blood disease, autoimmune skin disease, celiac disease, extra-hepatic autoimmunity, hepatitis C, immune thrombocytopenic purpura, Sjögren's syndrome and type 1 diabetes mellitus[15,20,32]

Diagnosis, prognostic markers and treatments

- Patients are largely asymptomatic at diagnosis,[2,3,25,33,34] which often occurs during follow-up of pre-existing IBD[33,35,36]
- Independent studies show that low alkaline phosphatase (ALP) levels (ALP < 1.5 upper limit of normal) are associated with better short-term prognosis[2,37] and that patients with increased ALP levels experience a higher risk of cancer, death or liver transplantation (LT)[12,38–40]
- Based on the limited data identified in the structured literature review, the prognostic role of fibrosis in PSC is not fully understood
- Pharmacological management focuses on control of symptoms and progression. Ursodeoxycholic acid is the most frequently prescribed treatment in PSC with rates ranging between 50% (US) and 82% (Australia)[15,41–43]

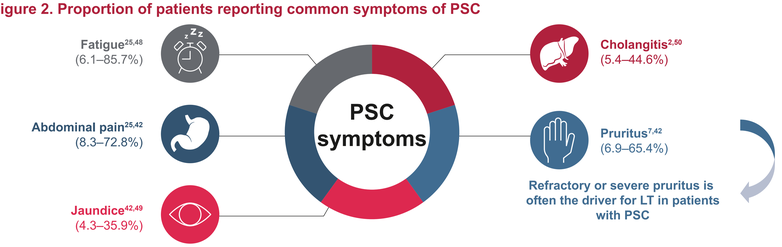
HRQoL and PROs

- Pruritus is a common symptom in patients with PSC (6.9–65.4%)[7,42] that severely impacts patients' HRQoL[44–46] and often becomes the driver for LT.[2,47,48] Other commonly reported symptoms include fatigue (6.1–85.7%),[25,48] jaundice (4.3–35.9%),[42,49] abdominal pain (8.3–72.8%)[25,42] and cholangitis (5.4–44.6%)[2,50] (**Figure 2**)
- The 36-Item Short Form Survey is the most frequently used tool to assess HRQoL in patients with PSC.[44–46] Independent studies from several countries show that patients with PSC report lower HRQoL than healthy controls,[44–46,51,52] with symptomatic patients having worse HRQoL than asymptomatic patients[44,46,53,54]

Natural history, disease progression and clinical and economic burdens

- The majority of studies reported all-cause mortality for patients with PSC between 10% and 20%,[2,5,7,14,17,25,27,42,50,55–63] although there were large variations (2–52%) across the studies[13,47]
- Around 15% of patients with PSC undergo LT,[2,9,42,59,60,82,83] with LT-related mortality contributing to the overall clinical burden of PSC. LT wait-list mortality spans from 5.3% to 26.4%,[84–87] whereas post-LT mortality ranges from 9% to 43%[5,58,62,66,88]

Figure 2. Proportion of patients reporting common symptoms of PSC



LT, liver transplantation; PSC, primary sclerosing cholangitis.

- Patients with PSC are four times more likely to develop cancer (including hepatobiliary cancer) than the general population[23] (**Figure 3**). A US study assessing hospitalizations and healthcare resource utilization due to PSC-associated malignancies estimated that total costs per hospitalization increased from US$32,480 (2001) to US$100,297 (2016), despite length of stay and mortality not increasing within that time frame. The increase was possibly due to more frequent use of diagnostic and therapeutic interventions to manage PSC and increased treatment modalities for hepatocellular carcinoma and colorectal cancer[64]
- Total costs associated with LT within the first year after surgery have been estimated at US$482,057.01 (2014 US$).[89] In a German retrospective study analyzing the resource utilization of patients undergoing LT across multiple indications, PSC was found to have the highest median costs during wait-list time (€22,771; 2013 €). This was mainly due to clinical evaluation costs, especially ERCP.[90] Post-LT, PSC had the second highest outpatient costs (€4,447; 2013 €)
- Although reported rates varied widely (7–72.1%), most studies showed that approximately 20% of patients who undergo LT experience disease recurrence,[33,47,55,58,62,65,67,69,75,84,85,88,91–107] which usually has a worse prognosis than the primary disease.[108–110] Survival was found to be significantly lower in recurrent PSC (rPSC) (hazard ratio 2.28; $p < 0.001$) and liver re-transplantation rates were significantly higher (34% vs 14%; $p < 0.001$) than in patients with non-rPSC.[110] Additionally, rPSC was associated with an increased risk of cancer recurrence and graft failure[62,94,103,108,109,111]
- Comorbidities may increase the clinical burden of PSC: patients with comorbid PSC and IBD were more likely to have extensive UC and colorectal, hepatobiliary and extrabiliary cancers than patients with IBD alone.[59,65,72,73,81,112] Patients with PSC and UC were diagnosed with cholangiocarcinoma more often than patients with UC alone.[73,113] Studies assessing the impact of concomitant UC or IBD on direct costs associated with PSC show conflicting results: some report similar hospital costs and length of stay data, while others report higher hospitalizations and costs in patients with these comorbidities[57,113–115]

Figure 3. Cancer incidence in patients with PSC

PSC, primary sclerosing cholangitis.

Conclusions

- **Patients with PSC experience daily symptoms and have both an increased risk of mortality and an increased risk of developing cancer than the general population; this results in lower HRQoL for this patient group**
- **The patient burden of PSC is substantially increased by the presence of autoimmune comorbidities**
- **A considerable proportion of patients require a liver transplant, which is associated with a high-cost burden**

Acknowledgments: This work was conducted by PRMA Consulting in partnership with Gilead. The authors thank Oxford PharmaGenesis, Melbourne, Australia for providing editorial support, which has been funded by Gilead Sciences, Inc., in accordance with Good Publication Practice (GPP 2022) guidelines.

Presented at ISPOR 2023, Boston, MA, USA, May 7–10, 2023