Risk Stratification through Clinical Phenotypes in Primary Sclerosing Cholangitis

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ABSTRACT

Background & Aims: Primary sclerosing cholangitis (PSC) is a rare hepatobiliary disorder associated with inflammatory bowel disease (IBD). Within a goal of stratified care delivery across varying presenting phenotypes, the International PSC Study Group evaluated the clinical course of PSC across the largest patient cohort ever assembled.

Methods: A retrospective study was conducted on patients diagnosed with PSC between 1980 and 2010 (37 centres, 17 countries). Clinical outcomes' assessment was stratified according to recognized phenotypic descriptors.

Results: Of 7,121 patients, 2,616 progressed to liver transplantation/death (LTD) (median 14.5 years); and 721 developed hepatopancreatobiliary malignancy, mainly cholangiocarcinoma (n=594) (incidence rate: 5.4 and 1.4 per-100-patient-years, respectively). 65.5% of patients were men, 89.8% had classical/large-duct disease, and 70.0% developed IBD. Assessing the development of IBD as a time-dependent covariate, Crohn's disease (CD) or IBD-absence (vs. ulcerative colitis (UC)) conferred lower risk of LTD (unadjusted hazard ratio [HR]:0.62, p<0.001; and HR:0.90, p=0.03) and malignancy (HR:0.68, p=0.008; and HR:0.77, p=0.004); as did small-duct PSC (sdPSC) vs. classical PSC (HR:0.30 and 0.15, both p<0.001), and female vs. male sex (HR:0.88, p=0.002; and HR:0.68, p<0.001). On multivariable analyses assessing LTD, the protective impact of sdPSC persisted for both sexes (adjusted HR for men and women: 0.23, p<0.001 and 0.48, p=0.003); whereas UC conferred increased risk of liver disease progression vs. CD or IBD-absence (HR:1.56, p<0.001; and HR:1.15, p=0.002).

Conclusions: Our internationally representative cohort demonstrates how phenotypic diversity impacts the clinical course of PSC, and provides clinical outcome estimates relevant to patient care and future trial design.

Keywords: Inflammatory Bowel Disease, Transplantation, Cholangiocarcinoma, Ulcerative Colitis, Crohn's Disease

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated liver disorder strongly associated with inflammatory bowel disease (IBD).[1] Although rare, PSC carries an ongoing and disproportionate clinical need, with clinical outcomes being determined by the development of end-stage biliary cirrhosis and an independent risk of hepatopancreatobiliary (HPB) malignancy. To date, medical therapies have not been effective,[8] and liver transplantation remains the only proven life-extending intervention, with 10 – 15% of all transplant activity in Europe now being performed for PSC.[5–7]

Accurately reporting the natural history of disease remains a critical challenge not only for clinicians, but also industry and regulatory agencies who collectively recognise the need for new therapies and equally appreciate the risks and obstacles in demonstrating patient-benefit against the background of an orphan disease with a relatively variable, often slow clinical course.[9] Moreover, patients seek reassurance and guidance as to their own prognosis, whereas clinicians wish to confidently recognize those at highest risk of poor outcomes as equally as they strive to reassure individuals with a more favorable prognosis.

To expand upon single-center and single-country descriptors, the International PSC Study Group (IPSCSG) sponsored a multi-center outcome study to model the natural history of the disease. Our primary aim was to evaluate and report the clinical course from a large internationally representative PSC cohort; which included 7,121 patients seen at 37 centres across 17 countries, and encompassing >30-years of clinical observation, 1,696 liver transplants, 920 deaths and 721 incidents of HPB malignancy. In so doing we not only validate the presence of key phenotypic descriptors, but also determine the extent of their interaction and how they may impact the clinical course that patients may experience.

PATIENTS AND METHODS

Study setting and design

We collected and analysed data from well-characterised patients diagnosed with PSC between January 1st 1980 and December 31st 2010, having previously attended or under current clinical follow-up until study completion (June 30th 2014). Any individual with an established diagnosis of PSC (including small-duct disease; sdPSC) in accordance with European or American recommendations[10–12] was considered eligible for inclusion. When biochemical, serological, and/or histological features of autoimmune hepatitis (AIH) were evident concurrently or sequentially,[13] the diagnosis of a PSC phenotype with AIH features (PSC/AIH variant) was made according to discretion of the participating center. IBD phenotypes were determined according to local expertise,[14–16] and classified as ulcerative colitis (UC), Crohn's disease (CD), or indeterminate colitis (IC), in keeping with consensus guidelines.[17,18]

Data collection

Identification of study participants was performed at a local level, either through a pre-existing and prospectively collected local PSC database; or in a retrospective manner via review of medical records by a named site investigator at a given institution. All individual center data was captured onto a multi-parametric standardised case record form formulated by the IPSCSG, and upon study completion amalgamated into a common 'master' database for downstream analysis. Individual clinical characteristics pertained to patient sex, clinician-reported age at and date of diagnosis of PSC, sub-phenotype and IBD phenotype, date and indication of IBD-related surgical resections, date of LT, date of death and date and type of first HPB malignancy. Patients with sclerosing cholangitis suspected due to alternate aetiologies (e.g. IgG4-related disease, acquired immunodeficiency syndromes, confirmed biliary transporter defects) were excluded from the analysis, as were those with inadequate/unknown

follow-up duration. Upon completion of data capture, all patient datasets were checked for plausibility and validity, and duplicated patient entries were removed prior to analysis.

Data interpretation and analysis

All patients were identified at time of diagnosis or during subsequent follow-up. 'Time zero' was set from point of diagnosis of first PSC phenotype, with the primary endpoint being the incidence rate (and associated risk) of LT, or death (LTD) in non-transplanted patients. Any individual not experiencing a clinical event in this regard was censored at date of last known follow-up. A secondary endpoint of HPB malignancy was also studied, and in this instance the date of first liver transplantation/death, or last date of 'event-free' follow-up comprised our censor points. Diagnosis of HPB malignancy was made according to clinical, radiological and/or histological findings as dictated by center-specific protocols.

Categorical variables are expressed as numbers (*n*), with percentages in parenthesis, and continuous data as mean ± standard deviation (SD) unless otherwise indicated. Statistical comparisons between groups were performed using Pearson's Chi-squared test. Differences in the means and proportions between individual groups of continuous data were assessed using the independent samples t-test, following Levene's test for equality of variances.[19] A p value less than 0.05 was considered statistically significant.

Univariate and multivariable Cox proportional hazards models were fit to assess the impact of individual covariates on the instantaneous rate of clinical events, with time-to-event analysis ascertained through Kaplan-Meier estimates. Given that the development of IBD does not parallel that of PSC, the independent prognostic impact of IBD-phenotype was assessed separately as a time-fixed as well as a time-dependent covariate. All individual covariates were assessed for statistically significant interaction terms, including patient demographic features

(age and sex) and individual phenotypic descriptors for PSC and IBD subtypes separately. All analyses were stratified by geographical region (Australia, North America, Northern Europe, Central Europe, Western Europe or Southern Europe) and adjusted for year of PSC diagnosis. Incidence rates were calculated by the life tables' method. Statistical analyses were performed with IBM SPSS Statistics 22.0 (SPSS Inc, Chicago, IL).

Ethical approval

This study was conducted in accordance with the protocol and principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local institutional ethical boards of all participating centers.

RESULTS

Study population

We accrued clinical data pertaining to 7,931 patients (53,983 patient-years); however, those with inadequate follow-up or indeterminate diagnosis of PSC were exempted from further analysis (**Figure 1**). The final patient cohort consisted of 7,121 patients; either having PSC in its classical form (89.8%), as small-duct disease (3.6%), or the PSC/AIH-variant (6.6%) (**Table 1)**. Observing the cohort in its entirety, the majority of patients were men (65.5%), with a mean age at diagnosis of 37 years versus 40 years in women (p<0.001). Seventy percent of all patients developed concomitant IBD prior to, at, or following PSC diagnosis; which under most circumstances was morphologically consistent with UC. However, the development of UC was less common in women than men (48.1% vs. 61.0%, respectively; p<0.001), and in those with variant PSC sub-phenotypes relative to classical PSC (frequency of UC in patients with classical PSC: 58.1% vs. 33.5% in sdPSC, and vs. 47.7% in PSC/AIH; p<0.001 for both pairwise comparisons) (**Supplementary Tables 1, 2** and **3**).

During the defined observation period, 20.2%, 37.0%, 52.3% and 63.6% of patients underwent liver transplantation or died at 5, 10, 15 and 20 years, respectively (**Figure 1**), yielding a median transplant-free survival time of 14.5 years (95% confidence interval [CI]: 13.6 – 15.2 years; **Figure 2A**). With regard to our secondary endpoint, 7.1%, 10.9%, 16.0% and 21.6% of the patient population developed a HPB malignancy at the aforementioned time points (**Figure 2B)** (overall n = 721).

The majority of HPB malignancy events were cholangiocarcinoma (CCA) (n = 594), and over one-third of all malignancies were detected in the first year following PSC diagnosis. The incidence of CCA increased with advancing age at PSC diagnosis (**Supplementary Figure 1**);

whilst hepatocellular carcinoma (n = 59) or gallbladder carcinoma (n = 58) were less frequent. Only ten patients across seven centers were diagnosed with pancreatic carcinoma. HPB malignancy developed most often in association with classical PSC, with only a small number of such events occurring in patients with sdPSC (1 CCA, 2 HCC, 1 pancreatic carcinoma) or PSC/AIH variants (12 CCA, 1 gallbladder carcinoma, 1 HCC). Overall, the development of HPB malignancy at any point during the clinical course was associated with a significantly increased risk of patient mortality (hazard ratio [HR]): 15.7, 95% CI: 14.12 – 17.34; p<0.001).

Clinical stratifiers for liver transplantation/death and HPB malignancy

The incidence rates of clinical events according to baseline phenotypic descriptors are provided in **Supplementary Tables 4 and 5.** By univariate analysis, older age at diagnosis was associated with significantly poorer transplant-free survival; whereas female sex, CD (relative to UC), and sdPSC (relative to classical PSC) were identified as being protective (**Supplementary Table 6A)**. No significant difference in transplant-free survival was observed between the PSC/AIH variant versus the classical PSC sub-phenotype (**Supplementary Figure 2A**), although patients with the former were at a low risk of developing HPB malignancy (**Supplementary Figure 2B**) (**Supplementary Table 6B**).

The number of patients with IBD increased during our observation period (from 3469 patients at baseline to 4985 patients by the end of our study). Given that intestinal disease onset did not necessarily parallel that in the liver, the impact of IBD was subsequently determined as a time-dependent covariate. In this context, both CD and an absence of IBD carried stratification properties of a lower risk PSC phenotype; whereas patients developing UC were at highest risk for disease progression, or future development of HPB malignancy (**Supplementary Table 6**).

Patient sex modifies the risk of liver disease progression in classical PSC

To verify the relative independence of predictive phenotypic features, a comparative multivariable evaluation was performed. Through multivariable Cox regression analysis the prognostic impact of advancing age at diagnosis, as well as protective influences of female sex, having small duct disease, or CD at time of PSC diagnosis, all retained statistical significance in terms of stratifying risk of liver disease progression (**Figures 3** and **4**).

Despite both factors being proven as independent risk-predictors, there was a statistically significant interaction (p=0.013) between patient sex and PSC sub-phenotypes when evaluating liver transplantation/death as an endpoint. To this effect, patients with sdPSC demonstrated significantly improved transplant-free survival, relative to same-sex counterparts with classical PSC and PSC/AIH, when matched for their age at PSC diagnosis as well as baseline IBD phenotype (**Figure 4A)**. These differences were retained when adjusting for the latter as a time-dependent covariate in our multivariable analysis (**Table 2A**). Although women more commonly exhibited non-classical PSC sub-phenotypes than men, statistically significant differences in the risk of LTD between the sexes were retained when restricting our analyses to only those patients with classical PSC (**Table 2B**).

Unlike our primary endpoint, no statistically significant interactions were evident between patient sex and PSC sub-phenotypes when determining future HPB risk; wherein being female continued to exert a small, yet independent protective effect (but not an additive one) to that provided by small-duct disease (**Figures 3** and **4**) (**Table 3A** and **3B**).

IBD phenotype as an independent predictor of clinical outcome in PSC

Crohn's disease (at time of PSC diagnosis) relative to UC continued to exert a protective influence with respect to transplant-free survival and the development of HPB malignancy,

irrespective of the effect exerted by sex and PSC sub-phenotype. Such impact was not demonstrated in the group without IBD at baseline (**Figure 4)**. However, when addressing the impact of IBD as a time-dependent covariate, both CD and IBD-absence retained independent stratifying properties of a lower-risk PSC population (**Tables 2C** and **3C**). No statistically significant interactions existed between the different IBD phenotypes, and either PSC sub-phenotype or patient sex.

Reciprocally, development of UC prior to, or that which manifest during the clinical course of PSC, significantly increased the risk of LTD by 56% and 15% relative to CD or IBD-absence, respectively (**Table 2C**), and of HPB malignancy by approximately 45% and 37%, respectively (**Table 3C**). Of all patients with UC, 18.0 % (n = 718) underwent colectomy before reaching a primary or secondary endpoint; however, no significant difference in outcome was evident in such individuals relative to those retaining an intact colon (HR for colectomy in terms of LTD and HPB malignancy: 0.90 (95% CI: 0.78 – 1.05; p = 0.187) and 0.81 (95% CI: 0.61 – 1.07; p = 0.14), respectively).

IBD phenotype overrides the prognostic impact of patient sex

The prognostic impact of IBD phenotype when assessed as a time-dependent variable negated the marginal protective influence of female sex. This means that although sex was an independent risk factor of both clinical endpoints statistically, there were no demonstrable differences in either primary or secondary outcomes between men and women when matched for IBD phenotype as a time-dependent variable (data not shown). Moreover, the lower prevalence of UC in women (**Supplementary Table 1**) may account partially for differences in liver disease progression between the sexes.

DISCUSSION

PSC is a disease with significant clinical and societal burden, and in recognition of the hurdles involved in developing effective new therapies for patients, it is essential that robust descriptions of disease course are generated.[2,3,4] In this study, we validate the critical importance of specific phenotypic variants (i.e., the more favourable prognosis that limited small-duct variants offers patients), the negative prognostic impact of ulcerative colitis on liver-related outcomes, and the high incidence of cholangiocarcinoma in the first year following PSC diagnosis.[22,2] In addition, it is shown that patients with PSC and overlapping AIH-features carry a similar risk of liver disease progression to those with a more classical PSC phenotype; although development of HPB malignancy appears to be a rare event in PSC/AIH-overlap, and also for patients with a young presenting age at PSC diagnosis. Furthermore, we were able to address the prognostic impact of IBD development as a time-dependent covariate, recognising that development of UC is a key stratifier of adverse hepatobiliary consequences in PSC. Conversely, IBD-absence, and CD in particular, confer prognostic favour independent of the other phenotypic risk factors described.

To date, sex-specific variations in clinical phenotype and correlations with patient outcomes in PSC have lacked robust definition. Large scale studies have demonstrated the negative prognostic impact of male sex in patients with related disorders such as primary biliary cholangitis (PBC); specifically an association with treatment non-response and a higher incidence of HPB malignancy.[23,24] As an immune-mediated disease PSC is somewhat atypical, with a propensity for 'most' patients being younger men. However, the sex-distribution of PSC appears more balanced if cholangiographic screening is applied to all IBD-patients irrespective of biochemical abnormalities or symptomatology.[25] In any event, utilising the large size of the

IPSCSG cohort, men with classical PSC are seen to carry a slight, albeit statistically significant increased risk of disease progression compared with women of matched phenotype.

Our analysis also demonstrates that women with PSC have a much lower prevalence of UC than men. This is important because IBD phenotype, particularly when determined as a time-dependent covariate, proves to be an independent risk factor for disease progression and may explain the observed differences in outcome between sexes. Conversely, patients without IBD or those having CD are at a comparatively lower risk of developing adverse events; a finding suggested previously in two single center studies, which we now validate convincingly.[14,16] Of note, the IPSCSG has recently demonstrated genetic distinctions between patients with PSC and IBD versus those with IBD alone.[26–28] Notwithstanding efforts to better understand clinical outcomes, our study further supports the need to improve IBD classification in PSC, particularly as the intestinal phenotype is often distinct compared to classical colitis descriptors,[15] and more so given that genetic signals in PSC/CD may be disparate to those with PSC/UC.[28,29] Of note, our study does not capture details pertaining to the precise distribution of intestinal inflammation; however, prior evidence suggests that CD in PSC is invariably localised to the colon, with isolated ileal disease being a seldom reported finding.[14,16]

No significant outcome differences are apparent between men and women with the variant PSC sub-phenotypes, and consequently patients with sdPSC irrespective of gender experience a relatively sedentary clinical course compared with classical PSC. Perhaps more striking, however, is the highly similar transplant-free survival rate seen for patients with classical PSC and those with the PSC/AIH variant. Accepting the caveat that PSC/AIH lacks a codified diagnostic criteria,[30] these observations challenge the view of PSC/AIH variants imparting a lesser disease burden.[31] Instead, our findings indicate that once overt sclerosing cholangitis has

manifest, liver disease may progress at a similar rate irrespective of the initial mode of disease presentation.

We also show how development of HPB malignancy (mainly CCA) manifests as a critical event in the clinical course of patients, particularly with advancing age at PSC diagnosis, and associated with significantly diminished patient survival. It is plausible that the reason for a third of CCA being identified within the first year following PSC diagnosis, is due to a delay in the latter's detection (length-time bias), and not being manifest until CCA is clinically overt. This observation highlights the need for improving CCA screening and surveillance, especially in high-risk PSC patients with coexisting UC. If better non-invasive surveillance methods for CCA surveillance became available, it could support the rationale for systematic screening for PSC in UC patients.[25] On the contrary, patients with small duct disease, perhaps indicative of PSC in an earlier form or of shorter duration, carry a lower risk of developing malignancy – as described previously.[22,2] While this observation was somewhat expected, patients with the PSC/AIH-variant are also noted to develop HPB malignancy infrequently. This could possibly be a result of a lower UC burden, [20,2,32,33] which as our data suggests, is itself an independent hazard for future carcinoma development. Furthermore, with only 10 cases during 51,500 patient years of follow-up we could not validate previous reports[37] of a significant increased incidence of pancreatic carcinomas, albeit accepting the clinical challenges that exist in differentiating distal cholangiocarcinomas from primary pancreatic lesions.

The natural history of PSC has previously been studied by some of the participating centers comprising the IPSCSG (**Supplementary Table 7)**, although these cohorts are estimated to constitute, at most, <50% of our current patient population. Whilst certain patient characteristics that we describe mirror those in population-based registries,[2] ours is highly representative of a specialist-center PSC experience. In light of our prolonged study period,

transplant-center 'designation' and organ allocation policies have evolved significantly across institutions over time. Thus, it is not possible to accurately discriminate clinical outcomes based solely on the division between transplant versus non-transplant centers as conducted in other settings.[2] Admittedly, we do not present a population based epidemiological study, and due to the fact that more than 95% of included patients derived from centers with contemporary liver transplant activity, a degree of referral bias cannot be discounted. This may also explain the relatively low prevalence of sdPSC in our cohort.

Given the retrospective nature of our study, the interval frequency of repeated cholangiography varied between centers, therefore exhaustive surveillance imaging may not have been performed to exclude progression of all small duct cases to classical PSC. Similarly, there is no universally accepted guideline for repeated screening colonoscopy in those without IBD, hence we cannot discount that sub-clinical colitis may have developed in a subset of patients classified as having no IBD. Of note, our reported colectomy rate was 18% in patients with UC, which mirrors the incidence reported in single-center studies, but is lower than that observed in population-based cohorts and prospective multi-center registries of UC alone.[34–36]

Our analyses were intentionally restricted to addressing the prognostic impact of well-defined patient phenotypes. Consequently data pertaining to laboratory variables, extent of strictures, intervals of surveillance imaging or specific pharmacological interventions (e.g. ursodeoxycholic acid and/or immunosuppression) fell outside of the current study's remit. Further large-scale investigation of therapeutic impact is of critical importance, given the inconsistently reported effects of these agents on disease progression and malignancy risk in PSC. [8] Additionally, as a systematic autopsy review was not performed from all mortality cases it is plausible that the incidence of HPB malignancy may in fact be higher than actually reported,[37] particularly as CCA cannot always be discriminated from more benign changes in

PSC.[38] We are also unable to classify all causes of death in our retrospective patient cohort, although previous studies indicate that mortality in PSC is invariably due to liver disease or a complication of coexisting IBD.[2,39] A further restriction due to the retrospective nature and prolonged follow-up period (since 1980) is the fact that serum IgG4-levels were not determined systematically in all patients. Therefore it is not possible to conclusively exclude IgG4 associated cholangiopathy within a subset of our population.

The IPSCSG study confirms significant phenotypic diversity across the global PSC patient population. The estimates provided for transplant-free survival and the lifetime risk of HPB malignancy, would facilitate appropriate patient counselling and also aid in the future evaluation of potential new approaches to malignancy screening. In a drive to limit heterogeneity in clinical trials, which currently group together individuals at a high-risk of disease progression (classical PSC and UC) together with patients at intermediate risk (CD or IBD-absence) and low risk (sdPSC), our data underpins a collaborative effort to better appraise future therapeutic ventures for this orphan disease. As a clear consequence of our findings, future clinical trials may now be able to stratify entry according to a combination of precise phenotypic risk factors, limit the heterogeneity within studied cohorts, and provide a more objective evaluation of therapeutic efficacy in specific patient groups.

Table 1: Summary of Patient Characteristics

No. of pts.	7121
No. of men	4661 (65.5%)
Age at diagnosis:	
- Mean	38.5 yrs. (SD: 15.5)
- ≤ 20 yrs.	940 (13.2%)
- 21 – 30 yrs.	1508 (21.2%)
- 31 – 40 yrs.	1617 (22.7%)
- 41 – 50 yrs.	1435 (20.2%)
- 51 – 60 yrs.	953 (13.4%)
> 60 yrs.	665 (9.3%)
- *unknown*	3 (0.04%)
PSC sub-phenotype:	
- classical PSC	6397 (89.8%)
- small duct PSC	254 (3.6%)
- PSC / AIH variant	470 (6.6%)
Diagnosis year:	
- 1980 – 1984	217 (3.0%)
- 1985 – 1989	424 (6.0%)
- 1990 – 1994	773 (10.9%)
- 1995 – 1999	1414 (19.9%)
- 2000 – 2004	1802 (25.3%)
- 2005 – 2010	2491 (35.0%)
IBD phenotype at baseline:	
- ulcerative colitis	2761 (38.8%)
- Crohn's disease	595 (8.4%)
- indeterminate colitis	113 (1.6%)
- no IBD	3082 (43.3%)
- unknown timing	503 (7.1%)
-unknown IBD status	67 (0.9%)
IBD phenotype at end of follow-up:	
- ulcerative colitis	3989 (56.0%)
- Crohn's disease	786 (11.0%)
- indeterminate colitis	210 (2.9%)
- no IBD	2069 (29.1%)
- unknown IBD status	67 (0.9%)

Table 2: Risk Stratification of Liver Transplantation / Death by Disease Phenotype

		Reference phenotype	Adjusted hazard ratio (95% CI)	p-value
A) **PSC phenotype**	*Male*			
	Small-duct PSC	vs Classical PSC	0.23 (0.13 – 0.40)	<0.001
	PSC/AIH variant	vs Classical PSC	0.73 (0.56 – 0.94)	0.015
	PSC/AIH variant	vs Small-duct PSC	3.18 (1.71 – 5.92)	<0.001
	Female			
	Small-duct PSC	vs Classical PSC	0.48 (0.29 – 0.77)	0.003
	PSC/AIH variant	vs Classical PSC	1.19 (0.91 – 1.54)	0.20
	PSC/AIH variant	vs Small-duct PSC	2.49 (1.45 – 4.27)	0.001
B) **Sex**	*Classical PSC*			
	Female	vs Male	0.84 (0.77 – 0.92)	0.022
	Small-duct PSC			
	Female	vs Male	1.76 (0.84 – 3.69)	0.13
	PSC/AIH variant			
	Female	vs Male	1.38 (0.97 – 1.97)	0.075
C) **IBD phenotype**	Crohn's disease	vs Ulcerative colitis	0.64 (0.54 – 0.75)	<0.001
	Indeterminate colitis	vs Ulcerative colitis	0.94 (0.71 – 1.26)	0.69
	No IBD	vs Ulcerative colitis	0.87 (0.79 – 0.95)	0.002
	Crohn's disease	vs no IBD	0.73 (0.62 – 0.87)	<0.001
	Indeterminate colitis	vs no IBD	1.10 (0.83 – 1.48)	0.51
	Indeterminate colitis	vs Crohn's disease	1.50 (1.09 – 2.07)	0.013

* All analyses are stratified by geographical region of diagnosis; adjusted for calendar year and age at diagnosis. Inflammatory bowel disease phenotype is defined as a time dependent covariate. Hazard ratios for PSC sub-phenotypes are presented separately for men and women, and separately for sex are presented separately for PSC sub-phenotype, given the presence of a significant interaction term between gender and PSC sub-phenotype ($p = 0.005$).

Table 3: Stratification of Hepatopancreatobiliary Malignancy Risk by Disease Phenotype

		Reference phenotype	Adjusted hazard ratio (95% CI)	p-value
A) PSC phenotype	Small-duct PSC	vs Classical PSC	0.19 (0.07 – 0.51)	0.001
	PSC/AIH variant	vs Classical PSC	0.31 (0.17 – 0.55)	<0.001
	PSC/AIH variant	vs Small-duct PSC	1.62 (0.52 – 5.04)	0.41
B) Sex	Female	vs Male	0.68 (0.57 – 0.82)	0.001
C) IBD phenotype	Crohn's disease	vs Ulcerative colitis	0.69 (0.52 – 0.92)	0.01
	Indeterminate colitis	vs Ulcerative colitis	1.03 (0.52 – 1.75)	0.931
	No IBD	vs Ulcerative colitis	0.73 (0.61 – 0.87)	<0.001
	Crohn's disease	vs no IBD	0.96 (0.71 – 1.29)	0.77
	Indeterminate colitis	vs no IBD	1.41 (0.82 – 2.44)	0.22
	Indeterminate colitis	vs Crohn's disease	1.48 (0.82 – 2.67)	0.20

* All analyses stratified by geographical region of diagnosis; adjusted for calendar year and age at diagnosis. Inflammatory bowel disease phenotype is defined as a time dependent covariate.

Figure 1: Study cohort

At time of analysis data were available for 7,931 patients. However, following exclusion of groups with an alternate diagnose or inadequate follow-up, the final study group consisted of 7,121 patients of which 2,616 underwent liver transplantation or died, with a total of 721 developing primary hepatopancreatobiliary malignancy.

Figure 2: Cumulative incidence of clinical events

Kaplan-Meier estimates of [A] liver transplant (LT)-free survival rate across the patient population; and [B] incidence of all hepatopancreatobiliary (HPB) malignancies. Notably, 37.8% (*n* = 272) of all HPB malignancies occurred in the first year of PSC diagnosis, with the vast majority being cholangiocarcinoma during this time (incidence rate in the first year after PSC diagnosis: 2.6 cases per-100 patient-years).

Patients with unknown transplantation, mortality or malignancy status at time of study completion were excluded from respective analysis.

Figure 3: Impact of Patient Age and Gender on Clinical Outcome

Cox plots with regard to liver transplantation (LT) or hepatopancreatobiliary (HPB) malignancy. All data are stratified by geographical region of referring center and year of diagnosis, presented according to patient age at diagnosis and weighted for patient gender, inflammatory bowel disease (IBD) phenotype at baseline, and PSC sub-phenotype [A + B]; or patient gender weighted for patient age at diagnosis, IBD phenotype at baseline, and PSC sub-phenotype [C + D].

Figure 4: Impact of Variant PSC Sub-phenotypes and IBD Phenotypes on Clinical Outcome

Cox plots with regard to liver transplantation (LT) or hepatopancreatobiliary (HPB) malignancy. All data are stratified by geographical region of referring center and year of diagnosis, presented according to PSC sub-phenotype weighted for patient age at PSC diagnosis, gender, and inflammatory bowel disease (IBD) phenotype at baseline [A + B]; or patient IBD phenotype at baseline weighted for age at PSC diagnosis, gender, and PSC sub-phenotype [C + D].

Contributors:

TJW, PJT, BEH and KMB contributed equally to the manuscript and were primarily involved in data collection, validation, analysis, and manuscript preparation. AB, GMH, THK and CPS contributed to the data analysis and the manuscript preparation. BEH was the official study statistician who conducted and supervised statistical analysis and data interpretation. TJW, PJT, MI, HL, CYP, KH, DG, MAF, H-UM, DT, RKW, JF, TM, OC, KS, KNL, SA, SPP, CL, AM, SN, CLB, AF, EH, KKY, PM, UB, DKH, AP, CNM, GND, BE, PI, CPB, GIK, CS, VZ, LF, FB, MM, BDJ, KS, CR, KJ, MBdV, FS, AC, MT, THK, ES, MM, CPS, KDL, GMH and KMB were all involved in patient recruitment and assembling individual center data. All authors read and approved the final manuscript before submission.

Declaration of interests

All authors declare no competing interests regarding this study.

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