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TITLE PAGE

Title: Prevalence of Primary Sclerosing Cholangitis in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis.

Running title: Primary Sclerosing Cholangitis in Inflammatory Bowel Disease: A Meta-analysis.

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Abbreviations:

CD	Crohn's disease
CI	confidence interval
ERCP	endoscopic retrograde cholangiopancreatography
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
MRCP	magnetic resonance cholangiopancreatography
OR	odds ratio
PSC	primary sclerosing cholangitis

UC ulcerative colitis

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ABSTRACT

Background & Aims: Although the association between inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) is well recognised, uncertainties remain about the magnitude of this problem. We conducted a systematic review and meta-analysis assessing prevalence of PSC in IBD to investigate whether type of IBD, how presence of PSC was defined, sex, disease extent or location, time period, or geographical location influenced prevalence.

Methods: MEDLINE, EMBASE, and EMBASE Classic were searched (from inception to 10th April 2021) to identify observational studies recruiting ≥50 adult patients with IBD reporting prevalence of PSC. Data were extracted, and pooled prevalence, odds ratios (OR), and 95% confidence intervals (CIs) calculated.

Results: Of 1204 citations, 64 studies were eligible, containing 776,700 patients. Overall, pooled prevalence of PSC in IBD was 2.16%, and was highest in South America and lowest in Southeast Asia. Pooled prevalence in patients with UC, CD, or IBD-U was 2.47%, 0.96% and 5.01%, respectively. Pooled prevalence was significantly higher in UC versus CD (OR = 1.69; 95% CI 1.24-2.29). In subgroup analyses according to method used to define presence of PSC, the highest prevalence was 2.88% in studies performing both liver biochemistry and ERCP/MRCP, and the lowest was 1.79% in studies using a clinical diagnosis. Prevalence was generally higher in men, patients with more extensive, compared with left-sided, UC or ileocolonic or colonic, compared with ileal, CD.

Conclusions: Our findings provide the first pooled estimates of the burden of PSC in IBD, as well as potential risk factors, which may be important in establishing a prompt diagnosis and initiating appropriate surveillance for relevant gastrointestinal malignancies.

Keywords: Extraintestinal Manifestations, Hepatobiliary Manifestations, Ulcerative Colitis, Crohn's Disease, Primary Sclerosing Cholangitis.

INTRODUCTION

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic remitting and relapsing diseases, with a significant impact on quality of life and social functioning, as well as psychological health.[1-4] Almost 50% of patients will develop extraintestinal manifestations during their lifetime, with a further impact on disease outcomes.[1,2,5] Among these manifestations, there are those affecting the hepatobiliary tract, such as primary sclerosing cholangitis (PSC), characterized by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts, with eventual evolution to cirrhosis and malignancy in the majority of patients.[6,7]

The precise aetiology of PSC remains elusive. However immunological mechanisms, immunogenetic susceptibility, and disorders of biliary epithelia are believed to be involved.[8] The diagnosis is made in the setting of chronic cholestatic liver biochemical abnormalities, in particular elevated serum alkaline phosphatase levels, along with cholangiographic evidence of multifocal strictures of intrahepatic and extrahepatic bile ducts.[6] Liver biopsy is recommended to establish a diagnosis in patients with suspected small duct PSC to exclude other conditions.[6] Common symptoms include itch and lethargy, although many patients are asymptomatic, even those with advanced disease.[6]

PSC can precede the diagnosis of IBD, although some patients are diagnosed several years after panproctocolectomy for UC.[9] Estimated prevalence rates in patients with IBD vary greatly, by up to 10% in some studies.[10] Studies suggest PSC is diagnosed in 8% and 3.5% of patients with UC and CD, respectively.[10,11] In contrast, the presence of IBD, typically UC, has been reported in 80% of patients with PSC.[12] Even though the association between IBD and PSC is well recognised and has been studied widely,[13] uncertainties remain about the magnitude of this problem, as well as the strength of the relationship between PSC and type of IBD, disease extent or location, and sex.

A prior systematic review examined prevalence of, and risk factors for, hepatobiliary manifestations of IBD, including PSC, but the literature search only included studies up to 2014.[14]

In addition, a meta-analysis was not done and pooled prevalence estimates were not calculated. We have, therefore, conducted a systematic review and meta-analysis to assess prevalence of PSC in adult patients with IBD. We also aimed to investigate whether type of IBD, disease extent or location, sex or how presence of PSC was defined influenced prevalence rates, as well as whether prevalence varied according to geographical location of the study.

METHODS

Search Strategy and Study Selection

We searched EMBASE CLASSIC and EMBASE (from inception to 10th April 2021), and MEDLINE (from inception to 10th April 2021) to identify cross-sectional surveys or case-control studies reporting prevalence of PSC in unselected adult patients (≥90% aged ≥18 years) with histologically or radiologically confirmed IBD. Studies had to recruit ≥50 participants, and report prevalence of PSC. Studies recruiting a highly selected sample of patients, such as only those with a pouch or with known colonic dysplasia or neoplasia, were ineligible. These eligibility criteria, which were defined prospectively, are provided in Box 1.

We searched the medical literature using the following terms: *ulcerative colitis or colitis, Crohn's disease, inflammatory bowel diseases* (both as a medical subject headings and free text terms). We combined these using the set operator AND with studies identified with the following free text terms: *primary sclerosing cholangitis, hepatobiliary adj5 manifestations, extraintestinal adj5 manifestations*. There were no language restrictions. We screened titles and abstracts of all citations identified for potential suitability and retrieved those that appeared relevant to examine them in more detail. Foreign language papers were translated. To identify potentially eligible studies published only in abstract form conference proceedings (Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week) were hand-searched. A recursive search of the literature was performed using bibliographies of all relevant studies. Where there appeared to be multiple study reports from the same group of subjects, we contacted study authors to clarify this issue. We also contacted authors if a study appeared potentially eligible, but did not report the data required, to obtain supplementary information. We performed eligibility assessment independently. This was done by two investigators (BB and DM), using pre-designed eligibility forms. We resolved disagreements by consensus and measured degree of agreement with a kappa statistic. Ethical approval was not required.

Data Extraction

Data were extracted independently by two investigators (BB and DM) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA). Again, we resolved discrepancies by consensus. The following data were collected for each study: country, method used to define presence of PSC, number of subjects, number of male or female subjects, type of IBD (UC, CD, or IBD-unclassified (IBD-U)), number with proctitis and proctosigmoiditis, left-sided UC, or extensive UC, number with ileal, colonic, or ileocolonic CD, or with isolated CD of the upper gastrointestinal tract, number with CD with inflammatory, stricturing, or penetrating disease, number (IBD, UC, CD or IBD-U) with concomitant PSC, number of males or females with PSC, number with proctitis and proctosigmoiditis, left-sided UC, or extensive UC with PSC, number with ileal, colonic, or ileocolonic CD, or with isolated CD of the upper gastrointestinal tract with PSC, and number with CD with inflammatory, stricturing, or penetrating disease with PSC.

Data Synthesis and Statistical Analysis

We combined the proportion of patients with IBD with concomitant PSC in each study to give a pooled prevalence for all studies, using a random effects model to provide a conservative estimate of prevalence of PSC. We assessed heterogeneity between studies using the I^2 statistic, which ranges between 0% and 100%. Values of 25% to 49%, 50% to 74%, and ≥75% are considered low, moderate, or high levels of heterogeneity, respectively.[15] We conducted subgroup analyses according to IBD subtype (UC, CD, or IBD-U), extent or location of IBD according to the Montreal classification,[16] sex, geographical region, method used to define presence of PSC, and year of publication (1980-1990, 1991-2000, 2001-2010, 2011-2015, 2016-2020). In addition, we performed the same subgroup analyses according to method used to define presence of PSC, where there were sufficient studies to conduct these. Finally, we compared prevalence of PSC according to sex, type of IBD (UC, CD, or IBD-U), and disease extent or location using an odds ratio (OR), with a 95% confidence interval (CI). We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire,

England) to generate Forest plots of pooled prevalence and pooled ORs with 95% CIs. We planned to assess for evidence of publication bias by applying Egger's test to funnel plots of ORs,[17] where ≥10 studies were available.[18]

RESULTS

The search strategy generated 1204 citations. From these, 87 appeared relevant. In total, 64 fulfilled the eligibility criteria (Figure 1)**,** containing 776,700 subjects recruited from 30 different countries worldwide.[10,11,19-80] Almost all studies were conducted in a single country, except for a study conducted in Korea, Malaysia, Vietnam, Thailand, and Myanmar.[79] Eighteen studies recruited only patients with UC,[11,19-21,23,25-28,31,40,42,44,45,57,60,68,70] and three only patients with CD.[30,37,39] No study recruited only patients with IBD-U, although three reported prevalence of PSC for patients with IBD-U separately.[10,63,80] No study reported extractable data on prevalence of PSC in patients with CD according to disease behaviour. Agreement between investigators for study eligibility was good (kappa statistic = 0.74). Detailed characteristics of all included studies are provided in Supplementary Table 1.

Pooled Prevalence of PSC in Patients with IBD

The pooled prevalence of PSC in patients with IBD, based on 64 studies, which contained 776,700 patients was 2.16% (95% CI 1.76%-2.60%; I^2=99.1%, p<0.0001) (Table 1).[10,11,19-80]

The lowest prevalence of PSC reported in patients with IBD was 0.12% in one Korean study,[66] while the highest was 10.97%, reported in a Finnish study (Supplementary Table 1 and Figure 2).[10] Overall, the highest pooled prevalence of PSC in patients with IBD was observed in South America (3.83%; 95% CI 2.48%-5.46%, I^2=64.3%, p=0.06), and the lowest in Southeast Asia (0.60%; 95% CI 0.34%-0.94%, I^2=94.1%, p<0.0001) (Table 2). Heterogeneity persisted, even when studies were pooled separately according to year of conduct. Pooled prevalence peaked in studies published from 2001 to 2010 (Table 2). Eight studies reported prevalence of the small duct variant of PSC in patients with IBD and PSC.[10,26,28,30,32,33,42,61] Overall, pooled prevalence of small duct PSC in patients with IBD and PSC was 19.70% (95% CI 7.91%-35.16%; I^2=77.2%, p<0.0001).

When we considered UC, CD, or IBD-U separately, pooled prevalence of PSC was 2.47% (95% CI 1.92%-3.08%; I^2=99.2%, p<0.0001) in 43 studies containing 566,178 patients with

UC,[10,11,19-29,31-33,36,40-42,44,45,47-50,52,56-61,63,66,68-70,72,74,78-80] 0.96% (95% CI 0.69%-1.28%; I^2=91.7%, p<0.0001) in 28 studies recruiting 156,943 patients with CD,[10,22,24,29,30,32,33,36,37,39,41,47-50,52,56,58,59,61,63,66,69,72,74,78-80] and 5.01% (95% CI 1.26%-11.08%; I^2=98.7%, p<0.0001) in three studies containing 13,647 subjects with IBD-U (Table 1).[10,63,80] The OR in patients with UC, versus patients with CD, in 25 studies that reported prevalence in both UC and CD within the same study population, was 1.69 (95% CI 1.24-2.29), with moderate heterogeneity (I^2=66.5%, p<0.0001), but no funnel plot asymmetry (Egger test, p=0.36).[10,22,24,29,32,33,36,41,47-50,52,56,58,59,61,63,66,69,72,74,78-80] In patients with IBD-U, versus UC, it was 3.27 (95% CI 1.23-8.70; I^2=94.5%, p<0.0001), and in patients with IBD-U, versus CD, it was 4.73 (95% CI 1.62-13.75; I^2=92.9%, p<0.0001). Only three studies reported prevalence of small duct PSC in patients with UC or CD with PSC separately.[10,32,33] Overall, pooled prevalence of small duct PSC in patients with UC and PSC was 19.08% (95% CI 0.31%-51.06%; I^2=82.4%, p=0.003), and in CD and PSC it was 33.90% (95% CI 3.53%-75.59%; I^2=77.2%, p=0.02). The OR for small duct PSC in patients with CD, versus UC, within the same study population, was 3.41 (95% CI 0.77-15.05), with no heterogeneity between studies (I^2=0%, p=0.43). Finally, one study reported prevalence of small duct PSC in patients with IBD-U and PSC (20%).[10]

Pooled Prevalence of PSC in Patients with IBD According to Method Used to Define its Presence

Thirty studies used a clinical diagnosis of PSC, based on international classification of disease codes or patient records, in patients with IBD.[11,19,35,37-39,43,45,47,49-51,53,54,56,57,60,63-67,69-72,74,77,78,90] Pooled prevalence in these studies was 1.79% (1.26%-2.42%, I^2=99.5%, p<0.0001). Seventeen studies reported data separately in patients with UC[11,19,45,47,49,50,56,57,60,63,66,69,70,72,74,78,80] and 13 in CD,[37,39,47,49,50,56,63,66,69,72,74,78,80]

with a pooled prevalence of 1.73% (1.05%-2.57%, I^2=99.7%, p<0.0001) and 0.57% (0.34%-0.87%, I^2=93.9%, p<0.0001), respectively.

Twenty-five studies stated the diagnosis of PSC was made using a combination of liver biochemistry, magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), with liver biopsy in all patients with positive MRCP or ERCP or in selected cases with diagnostic uncertainty.[10,20-22,24-26,28-30,32,33,36,40-42,44,48,52,55,58,59,68,76,79] Pooled prevalence in these studies was 2.41% (1.79%-3.12%, I^2=93.0%, p<0.0001). Twenty-two studies reported data separately in patients with UC with a pooled prevalence of 2.82% (2.07%-3.68%, I^2=86.5%, p<0.0001),[10,20-22,24-26,28,29,32,33,36,40-42,44,48,52,58,59,68,79] while 14 studies reported prevalence in patients with CD (1.38%, 0.72%-2.25%, I^2=78.9%,p<0.0001).[10,22,24,29,30,32,33,36,41,48,52,58,59,79] When the diagnosis of PSC was reached using a combination of liver biochemistry and MRCP or ERCP, without liver biopsy, pooled prevalence was 2.88% (1.39%-4.89%, I^2=94%, p<0.0001) in eight studies.[23,31,34,46,61,62,73,75] Three studies reported data separately in UC[23,31,61] but only one in CD,[61] with a pooled prevalence of 5.10% (3.19%-7.44%, I^2=66.1%, p<0.052) and 11.0% (0.56%-18.8%), respectively (Table 2).

Prevalence of PSC in patients with IBD According to Sex

Twelve studies reported prevalence of PSC according to sex.[24-26,28-30,33,44,58,59,61,69] Pooled prevalence was higher in men with IBD (2.09%; 95% CI 1.04%-3.49%, I^2= 94.7%, p<0.0001) compared with women (1.79%; 95% CI 1.01%-2.79%, I^2= 90.3%, p<0.0001) (Table 2). The OR for men versus women with IBD, in these 12 studies, was 1.15 (95% CI 0.76-1.76) with moderate heterogeneity (I^2=57.6%, p=0.007) but no funnel plot asymmetry (Egger test, p=0.87). When analyses according to sex were conducted on nine studies in patients with UC, again, pooled prevalence was higher in men (2.79%; 95% CI 1.12%-5.19%, I^2= 95.9%, p<0.0001) compared with women (1.71%; 95% CI 0.84%-2.86%, I^2= 87.5%, p<0.0001).[24-26,28,33,44,52,58,69]

The OR for PSC in men versus women with UC, in these nine studies, was 1.47 (95% CI 0.84-2.58) with moderate heterogeneity between studies (I^2=68.1%, p=0.002) (Table 2). Similarly, prevalence was higher in men with CD (1.30%; 95% CI 0.29%-3.02%, I^2= 86.2%, p<0.0001) than women

(0.76%; 95% CI 0.16%-1.79%, I^2= 79.0%, p<0.0001) in five studies.[24,30,33,58,69] The OR in men versus women with CD, in the same studies, was 1.00 (95% CI 0.39-2.55) with moderate heterogeneity (I^2=45.8%, p=0.14) (Table 2).

Prevalence of PSC in patients with IBD According to Disease Extent or Location

Four studies reported prevalence of PSC in patients with UC or CD according to disease extent or location.[23,24,32,49] In UC, pooled prevalence was higher in those with extensive (5.38%; 95% CI 4.24%-6.65%; I^2= 0%, p=0.73) compared with left-sided UC (0.80%; 95% CI 0.23%-1.71%; I^2= 22.7%, p=0.27) (OR = 6.86; 95% CI 3.01-15.66) (Table 2). No patients with proctosigmoiditis in these studies had concomitant PSC. The OR for PSC in patients with extensive versus left-sided UC was 6.86 (95% CI 3.01-15.66), with no heterogeneity (I^2=0%, p=0.46). In patients with CD, pooled prevalence was higher in colonic (7.02%; 95% CI 1.25%-16.92%; I^2= 82.0%, p=0.0008) and ileocolonic (6.81%; 95% CI 2.01%-14.15%; I^2= 73.9%, p=0.009) compared with ileal disease (1.07%; 95% CI 0.07%-3.26%; I^2= 43.9%, p=0.15) (Table 2). No patients with isolated upper gastrointestinal disease in these studies had concomitant PSC. The OR in patients with colonic versus ileal disease was 3.52 (95% CI 0.68-18.27), with low heterogeneity between studies (I^2=36.5%, p=0.19), and for patients with ileocolonic versus ileal disease it was 3.78 (95% CI 0.76-18.74), again with low heterogeneity (I^2=43.2%, p=0.15).

Subgroup Analyses According to Method Used to Define Presence of PSC

Subgroup analyses of prevalence of PSC by sex, disease extent or location, geographical location, and year of publication according to method used to define its presence are provided in Supplementary Tables 2 to 4. Overall, prevalence was higher in men in studies using liver biochemistry and ERCP/MRCP with confirmatory liver biopsy if required, but higher in women in studies using a clinical definition or liver biochemistry and ERCP/MRCP. Prevalence was higher generally in extensive UC and in ileocolonic or colonic CD, irrespective of the definition used.

Finally, irrespective of the definition used, variation in prevalence according to geographical location and year of the study remained.

DISCUSSION

This systematic review and meta-analysis has assembled data from 64 studies reporting prevalence of PSC in IBD. We found a pooled prevalence in patients with IBD of 2.16%. Overall, the highest pooled prevalence in patients with IBD was observed in South America and the lowest in Southeast Asia. The pooled prevalence of PSC in UC or CD separately was 2.47% and 0.96%, respectively. In IBD-U, the pooled prevalence was 5.01%. The odds of PSC were 1.7-times higher in UC than CD. In IBD-U, the odds were 3.3-times higher than UC and 4.7-times higher than CD. In addition, we observed a higher prevalence of small duct PSC in CD compared with UC (33.90% versus 19.70%, respectively), with an almost four-times higher odds, although this was not statistically significant. When we performed subgroup analyses based on method used to define presence of PSC, the highest prevalence was observed in studies performing both liver biochemistry and ERCP/MRCP at almost 3%, and the lowest in studies using a clinical diagnosis at less than 2%. Pooled prevalence was generally higher in men with IBD compared with women, which remained the case when we analysed UC and CD separately. Pooled prevalence peaked in studies published from 2001 to 2010. In UC extensive disease seemed to be more strongly associated with PSC; no patients with proctosigmoiditis had PSC. Patients with extensive UC had a more than six-times higher odds of PSC compared with left-sided UC. In patients with CD pooled prevalence of PSC was higher in colonic or ileocolonic, compared with ileal, disease; no patients with isolated upper gastrointestinal CD had concomitant PSC. Although patients with CD with ileocolonic disease had an almost four-times higher odds of PSC than those with ileal disease this was not statistically significant. Most of these observations remained stable in subgroup analyses by sex, disease location or extent, geographical location, and publication year according to the method used to define presence of PSC.

We used a contemporaneous search strategy to maximise likelihood of identifying pertinent literature. Judging of study eligibility and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. We used a random effects model to pool

data to provide a more conservative estimate of prevalence of PSC in IBD and assessed for publication bias, where sufficient studies existed. Finally, to minimise influence of heterogeneity on our results, we performed extensive subgroup analyses.

Weaknesses include significant heterogeneity between studies in many analyses, which in many instances was not explained by subgroup analyses. Heterogeneity was reduced in subgroup analyses according to disease extent or location, although this may be because there were fewer studies, with reduced power to detect heterogeneity. However, given that heterogeneity persisted even when the analysis was limited by method used to define presence of PSC, type of IBD, sex, publication year, and geographical region, this suggests the observed variation between studies is genuine, and relates to other factors not examined by individual studies. Other limitations include the paucity, or absence, of studies reporting prevalence of PSC for some geographical regions. One should, therefore, be cautious when making comparisons between them. Although we were careful to avoid duplicate publications, we included several large national database studies. We cannot exclude potential overlap of cases in these studies with those from smaller studies conducted in the same countries. In addition, given the low pooled prevalence of PSC in IBD observed, studies with a smaller sample size are more likely to have provided extreme results that are odds with the true prevalence of PSC in IBD, and which may have impacted on some of our geographical estimates. Furthermore, the prevalence of PSC was greater in studies that used a combination of liver biochemistry and MRCP and/or ERCP, with confirmatory liver biopsy if required, than those that used diagnostic codes. The former is likely to be more accurate, and as the latter were used in some of the largest studies, again this may have affected some pooled estimates. Moreover, PSC can precede the diagnosis of IBD and can also occur many years after a diagnosis of IBD; this could contribute to an underestimation of its true prevalence in IBD. Finally, no included study had extractable data on prevalence of PSC in CD according to disease behaviour.

A previous systematic review evaluated the epidemiology of various hepatobiliary manifestations of IBD, including PSC, in patients with IBD.[14] However, a meta-analysis was not

done and pooled prevalence was not estimated. Prevalence in patients with UC ranged from 0.7% to 5.4%, in 12 studies, with a male predominance (3% in men versus 1% in women). Moreover, prevalence in CD, based on only three studies, ranged from 1.2% to 3.4%, with a similar prevalence in men and women (0.4% versus 0.3%, respectively).[14] Our meta-analysis assessed pooled prevalence of PSC in IBD in 64 studies and in UC, CD, or IBD-U separately in 43, 28, and three studies, respectively. Prevalence of PSC was higher in men compared with women both in UC and CD. Therefore, men with IBD seem more prone to concomitant PSC than women, in contrast to other autoimmune conditions, including Sjögren's syndrome, primary biliary cholangitis, thyroid disease, or systemic sclerosis.[81] This higher prevalence in women may be partly attributable to the X chromosome, which has many genes relating to the immune system.[82] Moreover, we also evaluated pooled prevalence of PSC in IBD according to disease extent and location, finding a higher prevalence in more extensive UC and in CD with colonic involvement. Our findings support previous suggestions that the co-occurrence of PSC and IBD is associated with a distinct IBD phenotype.[83-85] In fact, prior studies[83,84] and a systematic review,[85] report patients with PSC and IBD have an increased incidence of extensive colitis, rectal sparing, and backwash ileitis. Therefore, irrespective of disease type, extensive colonic involvement is the primary phenotype associated with PSC. In patients with CD, as previously demonstrated,[83] the highest prevalence of PSC was in colonic, followed by ileocolonic, disease, while prevalence in patients with isolated ileal disease was much lower.

Although PSC seems to be associated with a distinctive IBD phenotype, the effect of IBD on the natural history of PSC is less well defined. A retrospective case-control study revealed that major event-free survival, such as cancer, liver transplantation, or death was prolonged in patients with PSC and CD, compared with PSC and UC.[86] The authors suggested this finding may be explained by the increased prevalence of small duct PSC in CD compared with UC.[86] Eight included studies reported prevalence of small duct PSC among patients with both IBD and PSC, with a pooled prevalence of almost 20%. However, only three studies reported data in UC or CD

separately. We observed that one-in-five patients with PSC and UC and one-in-three patients with PSC and CD had a small duct variant, with an almost four-times higher odds of small duct PSC in CD, although this was not statistically significant.

When we performed subgroup analyses based on method used to define presence of PSC, the lowest prevalence was observed in studies using a clinical diagnosis, based on international classification of disease codes or patient records, while the highest was found in studies performing both liver biochemistry and ERCP/MRCP. However, the latter studies had assessment of the prevalence of PSC as their specific aim, performing either ERCP or MRCP in all subjects,[61] or in all those with abnormal liver biochemistry.[23] Lunder and colleagues, for instance, performed MRCP in all patients included in their study, and found patients with PSC even among those with normal liver biochemistry.[61] Liver biochemistry within the normal range is not uncommon in patients with PSC,[87] and it is recognised that normalisation of liver biochemistry is associated with a more favourable prognosis.[88] In addition, PSC has a long subclinical phase of up to 38 years.[89] Potentially, our findings suggest that prevalence of PSC in IBD could be underestimated, given that patients with subclinical PSC may be undiagnosed. Although no medical therapy has been shown to alter prognosis of PSC, a prompt diagnosis might benefit patients with IBD and concomitant PSC, with regard to more intensive surveillance for development of colorectal dysplasia or carcinoma, cholangiocarcinoma, pancreatic carcinoma, liver cirrhosis, or hepatocellular carcinoma, given that these patients are at increased risk of all these conditions.[90-92]

Prevalence of PSC in IBD appeared to vary across different countries and geographical regions. Pooled results from all studies demonstrated the lowest prevalence in Southeast Asia, although in several of these studies the diagnosis was established based on registry data or patient records without recourse to endoscopy, radiology, or histology. However, when we restricted our analyses to studies performing liver biochemistry and ERCP/MRCP, with confirmatory liver biopsy if required, Southeast Asia still had the lowest prevalence of PSC. Analyses using the most rigorous definition of PSC found persistent geographical variation in prevalence, including a two-fold higher

presence in South Asia, suggesting a role for ethnic, genetic, microbial, dietary or other risk factors. These findings also suggest that using diagnostic codes alone to define PSC may be inaccurate, and potentially underestimates its prevalence in IBD. In support, we noted that prevalence was highest in studies published from 2001 to 2010, where many studies used the most rigorous methods to define PSC. Thereafter, where more studies used diagnostic codes, it decreased.

In conclusion, this systematic review and meta-analysis has demonstrated the global prevalence of PSC ranged from 0.96% in CD to 2.47% in UC. Men, patients with extensive UC, or CD with colonic involvement were more prone to a concomitant diagnosis of PSC. Prevalence varied, considerably in some instances, according to country, geographical region, year of publication, and how PSC was defined. Some differences in prevalence were found when the analyses were restricted to studies using the most rigorous method to define presence of PSC, rather than a clinical diagnosis based on diagnostic codes, suggesting the importance of adequate design of future studies in order to avoid an underestimation of this disease in IBD. However, even when uniform subgroup analyses were performed, prevalence varied substantially suggesting that this is due to true variation. Reasons for this variability are unclear and should be the subject of future research. These data provide the first pooled estimates of the burden of this condition in IBD and can be used to inform future healthcare planning, as well as to underline the importance of its detection. Clinicians who care for patients with IBD must recognise and carefully screen for PSC, as an early appropriate diagnosis is imperative to prevent complications.

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ROLE OF THE FUNDING SOURCE

None.

ETHICS COMMITTEE APPROVAL

Not required.

Box 1. Eligibility Criteria
Cohort studies or case control studies
Participants not specially selected
Recruited adults (aged ≥16 years) with histologically or radiologically confirmed inflammatory bowel disease (Crohn's disease, ulcerative colitis, inflammatory bowel disease-unclassified).
Reported prevalence of primary sclerosing cholangitis in patients with inflammatory bowel disease
Sample size of ≥50 participants

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FIGURE AND TABLE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Meta-analysis.

Figure 2. Prevalence of PSC in Patients with IBD Worldwide.

Table 1. Pooled prevalence of Primary Sclerosing Cholangitis in Patients with IBD According to Disease Type.

Table 2. Pooled Prevalence of Primary Sclerosing Cholangitis in Patients with IBD According to Method Used to Define its Presence, Sex, Disease Localization, Year of Publication, Region.

Table 1. Pooled prevalence of Primary Sclerosing Cholangitis in Patients with IBD According to Disease Type

Disease Type	Number of Studies	Number of Patients	Pooled Prevalence (%)	95% Confidence Interval	I^2	P Value for χ^2
IBD	64	776,700	2.16	1.76 – 2.60	99.1%	<0.0001
UC	43	566,178	2.47	1.92 – 3.08	99.2%	<0.0001
CD	28	156,943	0.96	0.69 – 1.28	91.7%	<0.0001
IBD-U	3	13,647	5.01	1.26 – 11.08	98.7%	<0.0001

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; IBD-U: inflammatory bowel disease unclassified.

Table 2. Pooled Prevalence of Primary Sclerosing Cholangitis in Patients with IBD According to Method Used to Define its Presence, Sex, Disease Localization, Year of Publication, Region.

	IBD	UC	CD
Method Used to Define Presence of PSC			
Number of studies (number of patients)	30 (719,172)	17 (550,326)	13 (151,518)
Prevalence in studies using a clinical diagnosis (95% CI) #	1.79% (1.26% – 2.42%)	1.73% (1.05% - 2.57%)	0.57% (0.34% – 0.87%)
Number of studies (number of patients)	25 (50,531)	22 (13,318)	14 (5,325)
Prevalence in studies performing both liver biochemistry and ERCP/MRCP, with confirmatory liver biopsy if required* (95% CI)	2.41% (1.79% - 3.12%)	2.82% (2.07% - 3.68%)	1.38% (0.72% - 2.25%)
Number of studies (number of patients)	8 (6,463)	3 (2,000)	1 (100)
Prevalence in studies performing both liver biochemistry and ERCP/MRCP (95% CI)	2.88% (1.39% - 4.89%)	5.10% (3.19% - 7.44%)	11.0% (0.56 – 18.8%)
Number of studies (number of patients)	1 (534)	1 (534)	0
Prevalence in studies performing both liver biochemistry and liver biopsy (95% CI)	2.06% (1.03% - 3.66%)	2.06% (1.03% - 3.66%)	N/A*

Sex			
Number of studies (number of men; number of women)	12 (31,555; 22,683)	9 (20,298; 15,228)	5 (9,862; 6,260)
Prevalence in men (95% CI)	2.09% (1.04% – 3.49%)	2.79% (1.12% – 5.19%)	1.30% (0.29% – 3.02%)
Prevalence in women (95% CI)	1.79% (1.01% – 2.79%)	1.71% (0.84% – 2.86%)	0.76% (0.16% – 1.79%)
Odds ratio for men vs. women (95% CI)	1.15 (0.76 – 1.76)	1.47 (0.84 – 2.58)	1.00 (0.39 – 2.55)
I^2 (P value for χ^2)	57.6% (0.007)	68.1% (0.002)	45.8% (0.14)
UC: Disease Extent			
Number of studies (number of patients with extensive UC; left-sided UC; proctosigmoiditis)	-	4 (1,346; 892; 313)	-
Prevalence in extensive UC (95% CI)	-	5.38% (4.24% – 6.65%)	-
Prevalence in left-sided UC (95% CI)	-	0.80% (0.23% – 1.71%)	-
Prevalence in proctosigmoiditis (95% CI)	-	0.00%	-
Odds ratio for extensive vs. left-sided UC (95% CI)	-	6.86 (3.01 – 15.66)	-
I^2 (P value for χ^2)	-	0.00% (0.46)	-
CD: Disease Location			

Number of studies (number of patients with ileal; colonic; ileocolonic; upper gastrointestinal CD)	-	-	4 (346; 280; 303; 31)
Prevalence in ileal CD (95% CI)	-	-	1.07% (0.07% – 3.26%)
Prevalence in colonic CD (95% CI)	-	-	7.02% (1.25% – 16.92%)
Prevalence in ileocolonic CD (95% CI)	-	-	6.81% (2.01% – 14.15%)
Prevalence in isolated upper gastrointestinal CD (95% CI)	-	-	0.00%
Odds ratio for colonic vs ileal CD (95% CI)	-	-	3.52 (0.68 – 18.27)
I^2 (P value for χ^2)	-	-	36.5% (0.19)
Odds ratio for ileocolonic vs ileal CD (95% CI)	-	-	3.78 (0.76 – 18.74)
I^2 (P value for χ^2)	-	-	43.2% (0.15)
Year of Publication			
Number of studies (number of patients)	4 (1,632)	4 (1,468)	1 (164)
Prevalence from 1980-1990 (95% CI)	2.83% (1.55% – 4.49%)	3.04% (1.63% – 4.86%)	1.22% (0.15% – 4.34%)
Number of studies (number of patients)	9 (5,580)	8 (4,677)	4 (882)

Prevalence from 1991-2000 (95% CI)	2.98% (1.86% – 4.37%)	2.85% (1.98% – 3.87%)	3.04% (0.38% – 8.11%)
Number of studies (number of patients)	12 (6,054)	7 (3,380)	6 (1,396)
Prevalence from 2001-2010 (95% CI)	3.57% (2.54% – 4.77%)	4.08% (2.50% – 6.03%)	2.11% (1.05% – 3.52%)
Number of studies (number of patients)	16 (13,072)	10 (6,480)	7 (2,594)
Prevalence from 2011-2015 (95% CI)	1.36% (0.91% – 1.90%)	1.58% (0.82% – 2.57%)	0.74% (0.31% – 1.36%)
Number of studies (number of patients)	23 (750,362)	14 (550,173)	10 (151,907)
Prevalence from 2016-2021 (95% CI)	1.73% (1.17% – 2.40%)	2.08% (1.27% – 3.07%)	0.51% (0.27% – 0.86%)
Geographical Region			
Number of studies (number of patients)	9 (281,516)	5 (279,560)	2 (845)
Prevalence in North America (95% CI)	3.58% (1.86% – 5.84%)	3.72% (1.32% – 7.27%)	1.99% (1.06% – 3.20%)
Number of studies (number of patients)	3 (2,277)	3 (2,077)	1 (200)
Prevalence in South America (95% CI)	3.83% (2.48% – 5.46%)	4.18% (2.56% – 6.17%)	1.50% (0.31% – 4.32%)
Number of studies (number of patients)	21 (344,047)	16 (208,671)	9 (120,049)
Prevalence in Northern Europe (95% CI)	2.61% (2.10% – 3.17%)	2.70% (2.09% – 3.39%)	1.09% (0.64% – 1.67%)

Number of studies (number of patients)	11 (39,394)	7 (3,299)	8 (2,762)
Prevalence in Southern Europe (95% CI)	0.99% (0.69% – 1.34%)	1.28% (0.63% – 2.14%)	1.01% (0.51% – 1.67%)
Number of studies (number of patients)	4 (1,952)	1 (250)	1 (164)
Prevalence in Africa (95% CI)	1.47% (0.64% – 2.65%)	3.20% (1.39% – 6.21%)	1.22% (0.15% – 4.34%)
Number of studies (number of patients)	4 (2,665)	2 (1,187)	1 (110)
Prevalence in Middle East (95% CI)	1.98% (1.40% – 2.64%)	1.92% (1.22% – 2.77%)	3.64% (0.99% – 9.05%)
Number of studies (number of patients)	5 (3,049)	3 (1,823)	3 (571)
Prevalence in South Asia (95% CI)	2.64% (0.58% – 6.13%)	4.06% (0.25% – 12.14%)	0.83% (0.02% – 3.83%)
Number of studies (number of patients)	7 (101,800)	6 (69,311)	3 (32,242)
Prevalence in Southeast Asia (95% CI)	0.60% (0.34% – 0.94%)	0.67% (0.37% – 1.04%)	0.16% (0.02% – 0.44%)

Based on international classification of disease codes or patient records.

*Liver biopsy was performed in all patients with positive MRCP or positive ERCP or that it was performed only in selected cases.

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; PSC: primary sclerosing cholangitis; CI: confidence interval; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography.