Hepatobiliary and pancreatic manifestations in inflammatory bowel disease: an umbrella review of meta-analyses

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Abstract

Background: Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), can affect the hepatobiliary system and pancreas, substantially impacting the life quality of patients.

Objectives: To evaluate the quality of evidence and comprehensively assess the validity of associations of IBD with hepatobiliary and pancreatic diseases.

Design: We performed an umbrella review of existing meta-analyses in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) recommendations.

Data sources and methods: We systematically searched PubMed, Embase, and Web of Science from inception to April 2024, to identify and appraise meta-analyses examining IBD and risk of hepatobiliary and pancreatic manifestations. Methodologic quality was assessed with A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) and the strength of evidence was graded according to prespecified criteria.

Results: A total of 14 meta-analyses of observational studies were included. The strongest-validity evidence suggested the significant associations between IBD and risk of gallstones (odds ratio (OR) = 1.72; 95% confidence interval (CI) = 1.40–2.12) and acute pancreatitis (OR = 3.11; 95% CI = 2.93–3.30). Highly suggestive evidence indicated a significantly increased risk of hepatobiliary cancer in UC (incidence rate ratio (IRR) = 2.05; 95% CI = 1.52–2.76) and CD (IRR = 2.31; 95% CI = 1.25–4.28). In addition, highly suggestive evidence indicated that IBD was associated with portal venous system thrombosis. Suggestive evidence showed a significantly higher prevalence of primary sclerosing cholangitis, non-alcoholic fatty liver disease, autoimmune hepatitis, and autoimmune pancreatitis in IBD patients than in the general population.

Conclusion: The associations between IBD and multiple hepatobiliary and pancreatic disorders showed varying levels of evidence and magnitude of risk. Further high-quality primary studies are needed to identify IBD patients who are more at risk and would benefit the most from screening and prevention programs.

Trial registration (PROSPERO): CRD42023451461.

Keywords: extraintestinal manifestations, hepatobiliary and pancreatic diseases, inflammatory bowel disease, prevalence, risk factors

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Background

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic relapsing disorders of the gut, with a significant impact on the quality of life and social functioning.[1] The prevalence of IBD varies

considerably across countries and is higher in North America and Europe.[2] Moreover, a steady increase in incidence has been reported over the last decades in Asia and South America, constituting a significant public health burden.[1,2] IBD is considered an immune-mediated multisystemic disorder since up to 50% of patients develop at least one extraintestinal manifestation during their lifetime.[3–7] Among these manifestations, there are those affecting the hepatobiliary system and pancreas,[8–11] including primary sclerosing cholangitis (PSC), non-alcoholic fatty liver disease (NAFLD), gallstones, autoimmune hepatitis (AIH), autoimmune pancreatitis (AIP), and different types of malignancy. These disorders can occur before or after the diagnosis of IBD and are usually not necessarily consistent with the activity of intestinal inflammation.[6,8,10] They can substantially impact the patient's life quality, sometimes more so than the intestinal disease. Although the precise etiology of hepatobiliary and pancreatic manifestations of IBD remains elusive, immunologic mechanisms, environmental factors, or genetic susceptibility are thought to be involved. Moreover, some diseases occur in parallel with the structural and physiological changes associated with IBD. The diagnosis can be made in the setting of chronic liver biochemical abnormalities, hyperamylasemia, or hyperlipasemia, along with abnormalities of the hepatobiliary system and pancreas morphology. Common symptoms include abdominal pain, jaundice, fatigue, and lethargy, although many patients are asymptomatic, even those with advanced disease.[12,13] Thus, management of IBD patients with hepatobiliary and pancreatic manifestations remains a clinical challenge. Consideration and surveillance of these comorbidities during IBD can inform treatment selection and decision, therefore improving patient outcomes.

The prevalence of hepatobiliary and pancreatic manifestations in patients with IBD is still uncertain. Many previous studies have focused on the association of the manifestations with medication,[14–18] which may overestimate the contribution of IBD disease itself. Many studies including systematic reviews and meta-analyses have been conducted during the past decades, sometimes providing conflicting or inconclusive results.[11,19] There is no systematic effort to appraise the quality and robustness of evidence. In this study, we performed an umbrella review to systematically assess the range and credibility of reported associations of hepatobiliary and pancreatic manifestations with IBD. We collated the relevant systematic reviews and meta-analyses, assessed the quality of the methodology used and the potential bias, and determined which associations are supported by robust epidemiologic evidence.

Materials and methods

Study design

This umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) recommendations.[20] The protocol was registered with PROSPERO (CRD42023451461).

Search strategy

We conducted a systematic search in PubMed, Embase, and Web of Science, from inception to April 20, 2024, to identify systematic reviews and meta-analyses of studies examining the extraintestinal manifestations of IBD (including CD and UC). To avoid missing any effect estimate, the search strategy was very broad and used the terms "inflammatory bowel disease (IBD)," "Crohn's disease (CD)," or "ulcerative colitis (UC)" combined with "systematic review" or "meta-analysis," using truncated terms and appropriate MeSH terms (Supplemental Data). We excluded conference abstracts, letters, and editorials. The reference lists of the retrieved meta-analyses were screened for additional eligible articles.

Eligibility criteria

The full text of potentially eligible articles was screened independently by two authors (R.H., Z.L.). Eligibility criteria include the following: (1) meta-analyses of systematic reviews and epidemiologic studies providing quantitative data; (2) meta-analyses investigating associations between IBD and its extraintestinal manifestations; (3) subjects of any age, ethnicity, or gender, in any country and setting; and (4) full text available. Randomized controlled trials were unavailable for our research question. Exclusion criteria included the following: (1) studies on the inverse relationship between any disease and IBD; (2) studies on the comorbidities resulting only from drug or surgical treatment; and (3) studies on the relationship between intestinal microbiota and IBD.

Study selection and data extraction

Only systematic reviews with meta-analyses, which investigated associations of hepatobiliary and pancreatic manifestations with IBD, were included. When outcomes were investigated in only one meta-analysis, this study was selected for presentation. When multiple meta-analyses focused on the same condition, the consistency of the main findings was examined (same direction and similar magnitude of association). This approach has also been used in other published umbrella reviews.[21,22] Two independent reviewers (R.H. and Z.L.) screened the full text of potentially eligible articles and extracted data. Any discrepancies in the inclusion or exclusion of studies were resolved through discussion between the two reviewers. If a consensus could not be reached, a third reviewer (Y.D.) was consulted to make the final decision. For each meta-analysis, the following information was extracted: first author's name, publication data, specific IBD type (IBD/CD/UC), outcomes of interest (extraintestinal manifestations), number of primary studies synthesized, and study design. Details including the number of patients, any estimated value with a 95% confidence interval (CI), p value, and heterogeneity (I^2) were also extracted. We included studies reporting any effect size measure (risk ratio (RR), odds ratio (OR), incidence rate ratio (IRR), or standardized incidence ratio (SIR)). Because hepatobiliary and pancreatic manifestations of IBD are rare events, these measures of effect yield similar estimates. The extracted estimates were displayed as forest plots, illustrating the association between each manifestation and IBD.

Quality of meta-analyses and grade of evidence

We assessed the methodologic quality of the meta-analyses based on AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews).[23] AMSTAR 2 is a strict, validated, and reliable measurement tool that evaluates systematic reviews and meta-analyses. It consists of 16 items and includes ratings for quality in the search, reporting, analysis, and transparency of a meta-analysis, thereby categorizing the methodological quality as "high," "moderate," "low," or "critically low." In addition, the evidence of the correlation between IBD and hepatobiliary and pancreatic manifestations was classified into four categories: strongest validity (class I), highly suggestive (class II), suggestive (class III), and weak evidence (class IV) according to the criteria. The evidence with the strongest validity fulfills the following[24,25]: (1) statistically significant p value less than 0.05; (2) at least 1000 participants; (3) low or moderate between-study heterogeneity ($I^2 < 50\%$); (4) 95% CI that excludes the null value; and (5) no evidence of small-study effect and excess significance bias. The highly suggestive evidence meets criteria (1)–(4); the suggestive evidence meets (1) and (2); and the weak evidence meets only (1). The study with the highest grade of evidence was considered the most comprehensive. In cases of equal evidence grade, the study with more subjects was prioritized. When subject numbers were not reported, the study encompassing more studies was considered the most comprehensive.

Results

Characteristics of the recruited meta-analyses

The literature screening process according to PRISMA guidelines is shown in Figure 1. Two authors independently and systematically searched 8428 studies. After eliminating 3258 duplicates, 5170 articles were included in the initial review. After abstract screening and full-text screening, 14 meta-analyses of observational studies examining the prevalence or risk of hepatobiliary and pancreatic system manifestations among patients with IBD were included in this umbrella review. The publication dates ranged from 2010 to 2023. The number of original studies included in these meta-analyses ranged from only 2 to 118, and the sample sizes ranged from 5231 to 1,309,278 subjects. However, two studies did not provide the exact number of subjects. All the key information of included studies is displayed in Table 1, including study numbers, sample sizes, and clinical outcomes. Detailed characteristics of all included studies are provided in Supplemental Table 1. The hepatobiliary and pancreatic manifestations in patients with IBD included (n = number of meta-analyses) the following: PSC ($n = 2$),[19,26] NAFLD ($n = 4$),[19,27–29] gallstones ($n = 2$),[19,30] portal vein system thrombosis ($n = 2$),[19,31] pancreatitis ($n = 3$),[32–34] hepatobiliary and pancreatic cancers ($n = 4$),[19,35–37] AIH ($n = 1$),[19] and hepatitis B virus (HBV) infection ($n = 1$).[38] The prevalence and risk of different types of manifestations are shown in Figures 2 and 3 and Supplemental Table 2.

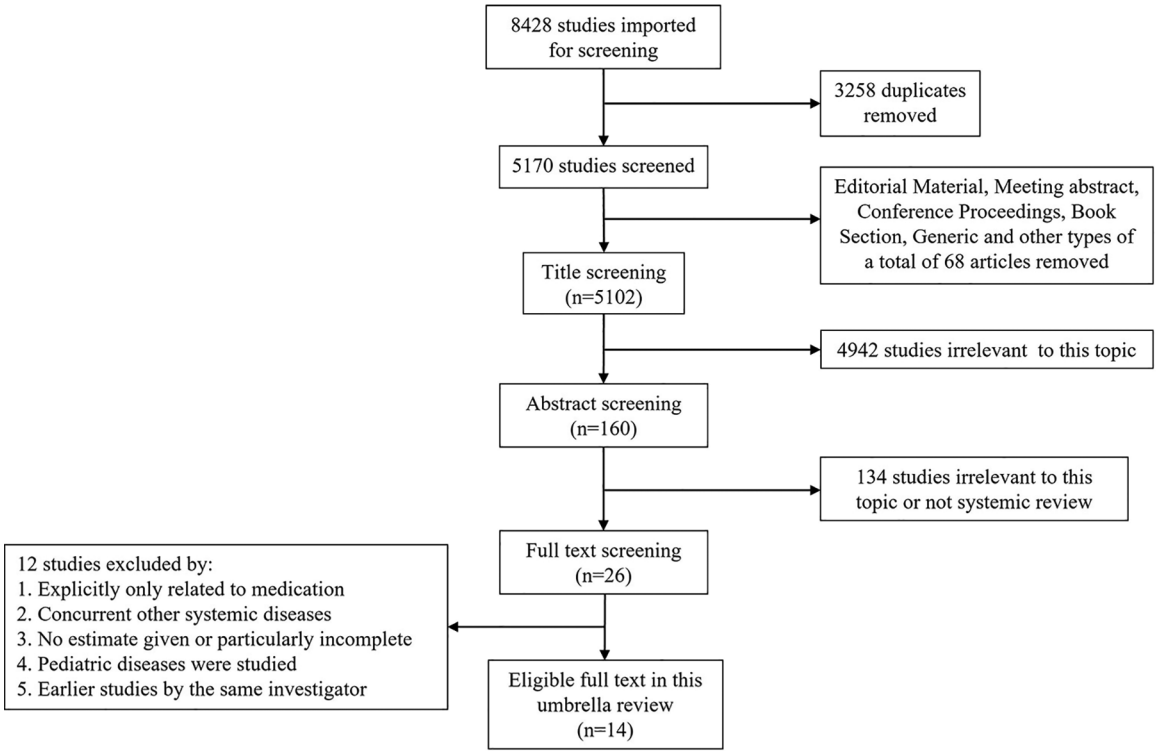

Figure 1. PRISMA diagram for selection of systematic reviews with meta-analyses.
PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

AMSTAR 2 and evidence grade classification

We assessed the methodological quality of each review using the AMSTAR 2 rating scale. All studies were categorized as critically low (12 studies) or low (2 studies) in methodological quality (Supplemental Table 3). The most common critical flaws were the absence of a registered protocol (8 studies) and non-satisfactory reporting/evaluation of the risk of bias in primary studies (10 studies). The grade of evidence for all studies was determined to be strongest validity (class I, three studies), highly suggestive (class II, two studies), or suggestive (class III, nine studies; Table 1).

Primary sclerosing cholangitis

The largest meta-analysis including 71 studies with 868,532 patients[19] revealed the estimated prevalence of PSC in the IBD population was 1.67% (95% CI = 1.47%–1.88%; I^2 = 99.1%; Figure 2),[19] which was remarkably higher than those in the general population (range from 0.008% to 0.03%).[39] Among all PSC patients, 68.1% (95% CI = 63.4%–72.8%; I^2 = 83.3%) had UC, and 29.4% (95% CI = 24.8%–34%; I^2 = 85.42%) had CD.[19] Another meta-analysis based on 64 studies containing 776,700 patients showed the pooled prevalence of PSC in IBD was 2.16% (95% CI = 1.76%–2.60%; I^2 = 99.1%; Figure 2).[26] The prevalence was significantly higher in patients with UC compared with patients with CD (OR = 1.69; 95% CI = 1.24–2.29; I^2 = 66.5%).[26] According to the criteria for classifying evidence strength, the grade of evidence in these two studies was suggestive (class III, with a statistically significant difference, enough participants, and high heterogeneity). In subgroup analyses on the disease extent or location, the prevalence was higher in patients with extensive versus left-side UC (OR = 6.86; 95% CI = 3.01–15.66; I^2 = 0%), and in colonic versus ileal CD (OR = 3.52; 95% CI = 0.68–18.27; I^2 = 36.5%) or in ileocolonic versus ileal CD (OR = 3.78; 95% CI = 0.76–18.74; I^2 = 43.2%).[26] According to the methods used to define the presence of PSC, the prevalence was higher in studies performing liver biochemistry and endoscopic

Table 1. Description of systematic reviews with meta-analyses included in the umbrella review.

First author	Country	Original article retrieval time	Number of studies	Disease type	Number of patients	Clinical outcome	Evidence grade
Beheshti Maal[19]	Iran	November 30, 2022	118	IBD	1,729,128	NAFLD, PSC, AIH, PVST, gallstone, cholangiocarcinoma	III
Giri[38]	India	April 1, 2022	34	IBD	26,745	HBV infection	III
Zamani[29]	America	September 30, 2021	44	IBD	14,947	NAFLD	III
Fukuda[32]	Japan	November 1, 2021	5	IBD	10,551	AIP	III
Lin[27]	America	April 1, 2018	27	IBD	7640	NAFLD	III
Barberio[26]	Italy	April 10, 2021	64	IBD	776,700	PSC	III
Lo[37]	Denmark	June 11, 2020	3	IBD/UC/CD	NA	Cancers	II
Lin[31]	China	November 3, 2021	11	IBD/UC/CD	29,527	PVST	II
Tel[33]	Hungary	June 19, 2019	8	IBD	1,309,278	Pancreatitis	I
Pedersen[34]	Denmark	October 1, 2018	3	IBD	77,314	Pancreatitis	I
Zou[28]	China	August 1, 2018	19	IBD	5620	NAFLD	III
Zhang[30]	China	February 1, 2015	5	IBD	5231	Gallstone	I
Huai[35]	China	December 1, 2013	4	IBD	129,859	Cholangiocarcinoma	III
Pedersen[36]	Denmark	January 1, 2009	7	UC/CD	NA	Cancers	III

AIH, autoimmune hepatitis; AIP, autoimmune pancreatitis; CD, Crohn's disease; HBV, hepatitis B virus; IBD, inflammatory bowel disease; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis; PVST, portal venous system thrombosis; UC, ulcerative colitis.

retrograde/magnetic resonance cholangiopancreatography (ERCP/MRCP) than in studies using a clinical diagnosis.[26]

Non-alcoholic fatty liver disease

The association of NAFLD with IBD was investigated in four meta-analyses, with consistent findings.[19,27–29] The level of evidence in these studies was suggestive (class III, with a statistically significant difference, enough participants, and high heterogeneity). The most comprehensive one included 38 studies with 228,216 subjects showed that the prevalence of NAFLD in IBD patients was 26.10% (95% CI = 22.10%–30.20%; $I^2 = 99.1\%$; Figure 2),19 which was comparable with the prevalence of 25.2% in the general population.[40] Among all NAFLD patients, the prevalence of UC was 41.7% (95% CI = 34.4%–49.1%; $I^2 = 88.13\%$) and the prevalence of CD was 56.7% (95% CI = 50.6%–62.8%; $I^2 = 80.92\%$).[19] Another meta-analysis performed by Lin et al.[27] includes 27 studies with 7640 individuals and showed a NAFLD prevalence of 32% (95% CI = 24%–40%; $I^2 = 98.24\%$) in IBD patients (Figure 2), which was higher than that of the general population. In addition, Zou et al.[28] included 19 studies with 5620 patients in their analysis and found the overall prevalence of NAFLD in IBD was 27.45% (95% CI = 20.72%–34.19%;

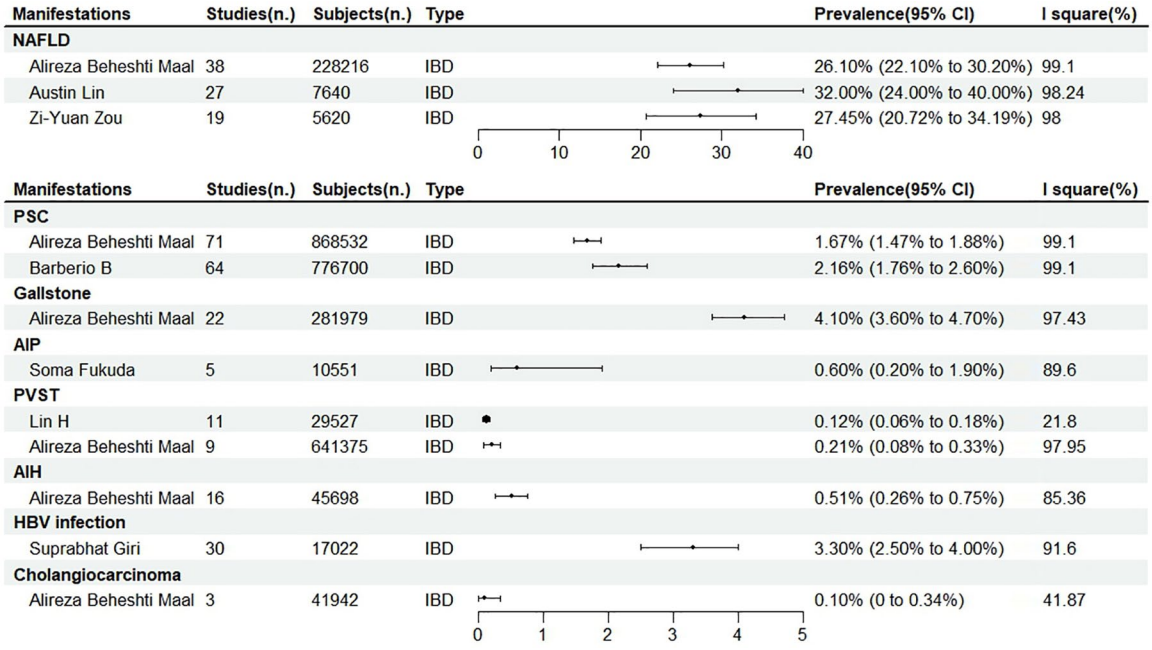

Figure 2. Forest plot shows the prevalence of hepatobiliary and pancreatic manifestations in IBD populations. The black circles and short lines represent the prevalence and 95% CI, with the size of the circle reflecting the grade of evidence.

AIH, autoimmune hepatitis; AIP, autoimmune pancreatitis; CI, confidence interval; HBV, hepatitis B virus; IBD, inflammatory bowel disease; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis; PVST, portal venous system thrombosis.

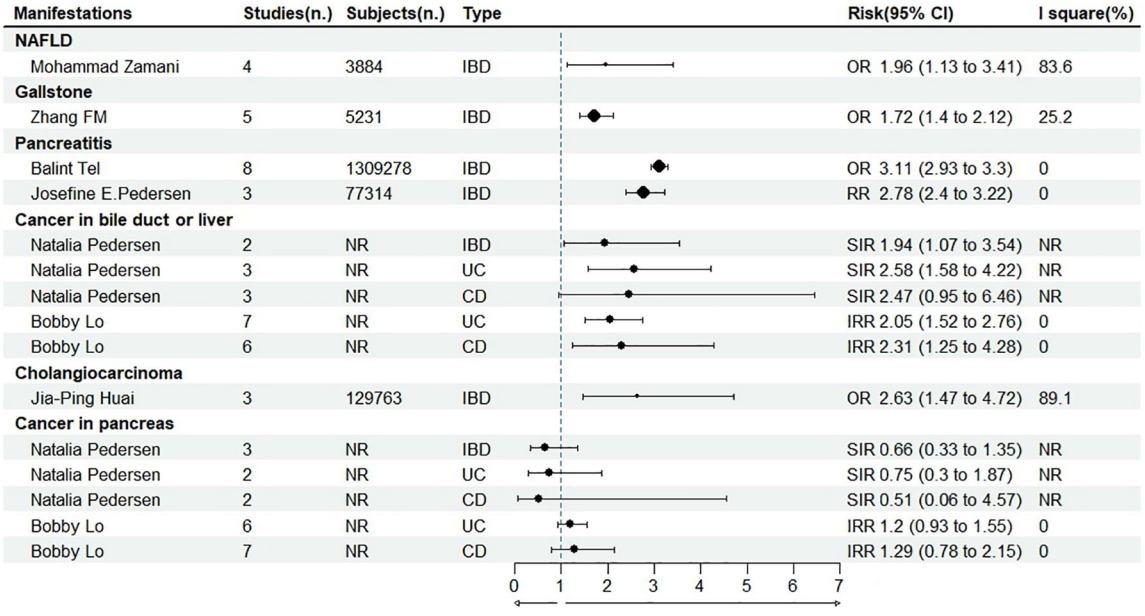

Figure 3. Forest plot shows effect estimates of meta-analyses reporting associations of IBD with hepatobiliary and pancreatic manifestations. The black circles and short lines represent the effect estimates and 95% CI, with the size of the circle reflecting the grade of evidence.

CI, confidence interval; IBD, inflammatory bowel disease; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; RR, risk ratio; SIR, standardized incidence ratio.

I^2 = 98%; Figure 2). Notably, Zamani et al.[29] included 44 studies comprising 14,947 subjects and showed that the global pooled prevalence of NAFLD was 30.7% (95% CI = 26.5%–34.9%; I^2 = 97.7%), and risk of NAFLD as almost two-fold higher in IBD patients versus healthy subjects (OR = 1.96; 95% CI = 1.13–3.41; I^2 = 83.6%; Figure 3). There was no significant difference in the OR of NAFLD in CD patients compared with UC patients (OR = 1.16; 95% CI = 0.93–1.44; I^2 = 63.9%).[29] Metabolic disorders such as diabetes, hypertension, insulin resistance, and metabolic syndrome were found to be risk factors for NAFLD in IBD.[28] Among the medications, methotrexate use (OR = 1.76; 95% CI = 1.02–3.06) increased the risk of developing NAFLD,[28] while corticosteroids, biologics, and parenteral nutrition were not associated with NAFLD.[28,29] There was no significant association between IBD phenotype (UC or CD), gender, disease activity, and the prevalence of NAFLD.[28,29] Furthermore, the most recent meta-analysis showed the prevalence of advanced liver fibrosis in 1012 IBD patients with NAFLD was 13.6% (95% CI = 7.6%–19.7%),[29] which was close to the prevalence of 10.3% (95% CI = 5.6%–15%) previously reported by Lin et al.[27]

Gallstone

The most recent meta-analysis (evidence grade of class III) included 22 studies with 281,979 subjects reported the prevalence of gallstone in patients with IBD was 4.10% (95% CI = 3.60%–4.70%) with high heterogeneity (I^2 = 97.43%; Figure 2).[19] Another study with the strongest validity evidence (class I, meeting all the required criteria) reported a significantly higher prevalence of gallstone in IBD patients than in control group (12.4% vs 9.6%, OR = 1.72; 95% CI = 1.40–2.12; Figure 3), and this trend was statistically significant in patients with CD (OR = 2.05; 95% CI = 1.61–2.63), but not those with UC (OR = 1.12; 95% CI = 0.75–1.68).[30] This study had lower heterogeneity (I^2 = 25.2%) and no significant publication bias (p = 0.805 for Egger's test).

Pancreatitis

Two meta-analyses assessed the risk of acute pancreatitis in patients with IBD,[33,34] with the strongest validity evidence (class I, meeting all the required criteria). The most comprehensive one by Tél et al.[33] included eight studies and revealed that IBD patients have a notably higher risk of acute pancreatitis compared with non-IBD population (OR = 3.11; 95% CI = 2.93–3.30; I^2 = 0; Figure 3) and the risk was significantly higher in CD (OR = 4.12; 95% CI = 3.75–4.54) than in UC (OR = 2.61; 95% CI = 2.40–2.83). Another analysis included four studies that showed an increased risk of acute pancreatitis in IBD patients, with an overall RR of 2.78 (95% CI = 2.40–3.22; Figure 3).[34] Both CD and UC patients had increased risk, with RR of 3.62 (95% CI = 2.99–4.38) and 2.24 (95% CI = 1.85–2.71), respectively.[34]

AIP and IBD are categorized into immune-mediated disorders. A separate meta-analysis included 5 studies with 10,551 IBD patients and revealed that the pooled prevalence of AIP was 0.6% (95% CI = 0.2%–1.9%; Figure 2).[32] The level of evidence in this study was suggestive (class III, with a statistically significant difference, enough participants, and high heterogeneity). Further analysis of AIP subtypes showed the ratio of type 1 and type 2 was 19.8% (95% CI = 12.6%–29.8%; I^2 = 44.9%) and 79.2% (95% CI = 69.1%–86.6%; I^2 = 45.3%), respectively.[32] Meanwhile, 40 studies with 4031 subjects showed the pooled prevalence of IBD was 10.5% (95% CI = 7.2%–15.0%) in AIP patients.[32] This study also demonstrated that patients with concomitant AIP and IBD had a significantly increased risk of AIP recurrence (RR = 1.9; 95% CI = 1.1–3.1) and colectomy (RR = 3.7; 95% CI = 1.9–6.9) compared with patients with either AIP or IBD, suggesting patients with both diseases had poor outcomes.[32]

Portal venous system thrombosis

Two meta-analyses investigated the association of IBD and portal venous system thrombosis (PVST).[19,31] Beheshti Maal et al.[19] included 9 studies with 641,357 patients and reported a PVST prevalence of 0.21% (95% CI = 0.08%–0.33%) in patients with IBD, but with high heterogeneity (I^2 = 97.95%) (evidence grade of class III; Figure 2). Another meta-analysis showed the prevalence of PVST was 0.12% (95% CI = 0.06%–0.18%; I^2 = 21.8%) in patients with IBD (Figure 2).[31] The grade of evidence in this study was highly suggestive (class II, with a statistically significant difference, enough participants, low heterogeneity, and reasonable CIs). Among IBD patients whose history of colorectal surgery was unclear, the prevalence of PVST was 0.99% (95%

CI = 0–2.74%; I^2 = 87.3%) in UC and 1.45% (95% CI = 0.26%–2.63%; I^2 = 91.6%) in CD, whereas among IBD patients who undergo colorectal surgery, the incidence of PVST was 6.95% (95% CI = 3.55%–10.36%; I^2 = 93.4%) in UC and 2.55% (95% CI = 0.27%–4.83%; I^2 = 49.3%) in CD, suggesting a higher probability of PVST after colorectal surgery.[31] In addition, preoperative corticosteroid treatment (OR = 3.112; 95% CI = 1.017–9.525) and emergency surgery (OR = 1.799; 95% CI = 1.079–2.998) were significant risk factors of PVST after colorectal surgery.[31]

Hepatitis

A single meta-analysis included 16 studies with 45,698 patients reported the prevalence of AIH was 0.51% (95% CI = 0.26%–0.75%; I^2 = 85.36%; Figure 2) in patients with IBD (evidence grade of class III),[19] which was significantly higher than those in the general population (range from 0.005% to 0.04%).[39] Among all AIH patients, 59.18% had UC (95% CI = 37.47%–80.88%) and 40.82% had CD (95% CI = 19.12%–62.53%).[19] A recent meta-analysis with suggestive evidence (class III, with a statistically significant difference, enough participants, and high heterogeneity) evaluated the prevalence of HBV and hepatitis C virus (HCV) infection in patients with IBD.[38] The pooled prevalence rates of HBsAg and anti-HCV in IBD patients were 3.30% (95% CI = 2.50%–4.00%; I^2 = 91.6%; Figure 2) and 1.8% (95% CI = 1.2%–2.4%; I^2 = 82.1%), respectively.[38] The odds of prevalence of HBsAg (OR = 1.08; 95% CI = 0.93–1.24) and anti-HCV (OR = 1.42; 95% CI = 0.93–2.18) were comparable between IBD patients and the general population.[38] Notably, only 35.6% (95% CI = 28.7%–42.4%; I^2 = 96.5%) of IBD patients had an effective HBV vaccination,[38] suggesting the screening and vaccination practices required to be improvement.

Cancer in bile ducts, liver, and pancreas

Four meta-analyses included hepatobiliary and pancreatic cancer in patients with IBD.[19,35–37] The most comprehensive study with highly suggestive evidence (class II, with a statistically significant difference, enough participants, low heterogeneity, and reasonable CIs) showed that both UC (IRR = 2.05 (95% CI = 1.52–2.76; I^2 = 0) and CD (IRR = 2.31; 95% CI = 1.25–4.28; I^2 = 0) patients had an increased overall risk of hepatobiliary malignancies (Figure 3).[37] Importantly, this meta-analysis showed a significantly increased risk of bile duct cancer among UC (IRR = 2.93; 95% CI = 1.73–4.98; I^2 = 0) and CD (IRR = 2.93; 95% CI = 1.16–7.41; I^2 = 0) patients,[37] although the increased risk of liver and pancreas cancer was not statistically significant.[37] Another meta-analysis with suggestive evidence (class III, with a statistically significant difference and enough participants) revealed a significantly increased risk of hepatobiliary cancer (SIR = 1.94; 95% CI = 1.07–3.54) in patients with IBD (Figure 3).[36] Furthermore, subgroup analysis showed a significantly increased risk of hepatobiliary cancer in UC (SIR = 2.58; 95% CI = 1.58–4.22) and a borderline increased risk (SIR = 2.47; 95% CI = 0.95–6.46) in CD patients (Figure 3).[36] Huai et al.[35] include 6 studies with 7838 subjects in their analysis (evidence grade of class III, with a statistically significant difference and enough participants) and reported a significantly increased risk of cholangiocarcinoma in patients with IBD (OR = 2.63; 95% CI = 1.47–4.72; I^2 = 89.1%; Figure 3), and this tendency was observed in both CD (RR = 2.69; 95% CI = 1.59–4.55; I^2 = 0) and UC (RR = 3.40; 95% CI = 2.50–4.62; I^2 = 0) patients. In addition, site-specific analyses revealed that IBD patients had an increased risk of intrahepatic cholangiocarcinoma (RR = 2.61; 95% CI = 1.72–3.95; I^2 = 72.5%) as well as extrahepatic cholangiocarcinoma (RR = 1.47; 95% CI = 1.10–1.97; I^2 = 22.0%).[35] Beheshti Maal et al.[19] include 3 studies with 41,942 patients reported the prevalence of cholangiocarcinoma in IBD patients was 0.1% (95% CI = 0–0.34%; I^2 = 41.87%; Figure 2). Two meta-analyses investigated the association of IBD and pancreas cancer,[36,37] but the results were not statistically significant. Pedersen et al.[36] were more inclined to support that the risk of pancreas cancer was decreased in both CD (SIR = 0.51; 95% CI = 0.06–4.57) and UC patients (SIR = 0.75; 95% CI = 0.30–1.87; Figure 3). By contrast, Lo et al.[37] showed a tendency of increased pancreas cancer risk in both CD (IRR = 1.29; 95% CI = 0.78–2.15) and UC (IRR = 1.20; 95% CI = 0.93–1.55) patients (Figure 3).

Discussion

IBDs are systemic diseases that manifest not only in the gut but also in the extraintestinal organs. This umbrella review of meta-analyses provided a comprehensive overview and assessment of the

prevalence or risk of hepatobiliary and pancreatic manifestations in patients with IBD. In evidence-based medicine, umbrella reviews are highly valued for their comprehensive and critical synthesis of meta-analyses and systematic reviews on a specific research topic, consolidating data from various sources and embodying the integration of evidence.[41] This umbrella review was carried out based on systematic methods including protocol registration, extensive literature searching through three scientific databases, independent study selection, and data extraction by two authors. Meta-analyses provide a quantitative synthesis of data, which allows for a more precise estimation of the effect and a better understanding of the strength of associations. Thus, we included only meta-analyses to obtain qualitative data on the hepatobiliary and pancreatic manifestations. We analyzed the sample size, prevalence rate, RR, or OR with 95% CIs and evaluated the heterogeneity and potential biases for each included meta-analysis. In addition, we assessed the methodological quality of the included meta-analyses and evaluated the strength classification of evidence for each outcome. The comprehensive nature of this umbrella review is unique given the breadth of hepatobiliary and pancreatic manifestations that were collectively assessed and summarized. Although some studies were excluded due to a focus on the medications or surgery-induced comorbidities, the use of broad criteria ensures that the conclusions are generally applicable to patients with IBD.

Among the hepatobiliary and pancreatic system manifestations of IBD, the most important is PSC, characterized by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts, with eventual evolution to cirrhosis, end-stage liver disease, and cholangiocarcinoma. We noted that the prevalence of PSC in IBD patients (1.67%–2.16%) was higher than in the general population (0.008%–0.03%),[19,26,39] and the prevalence was significantly higher in patients with UC compared with CD.[26] Patients with concomitant PSC and IBD usually have a male predominance and were more commonly characterized by extensive UC, and ileocolonic or colonic CD.[26] Due to the increased risk of end-stage liver disease, IBD-PSC patients may need a liver transplant 10–15 years after diagnosis of PSC. Moreover, IBD-PSC patients have a 10-fold increased risk for developing colorectal cancer compared with IBD patients who do not suffer from PSC.[8] Importantly, using liver biochemistry and ERCP/MRCP to define PSC could be more sensitive than using a clinical definition. These data suggested that PSC may be underdiagnosed due to the subclinical symptoms or lack of biochemical findings that characterize the early stage of the disease; therefore, a prompt diagnosis and intensive surveillance might benefit patients with IBD and concomitant PSC. Several mechanisms might be involved in the association between IBD and PSC, including genetic susceptibility, bacterial translocation, intestinal toxins, and immunity dysregulation.[42] It has been reported that patients with IBD may carry a susceptibility gene for PSC, such as HLA-DR3/HLA-DQ2.[43–45] Some mucosal lymphocytes in the gut during active inflammation persist as long-lived memory cells and could recirculate between gut and liver. These dual-homing lymphocytes might become activated in the liver and trigger cholangitis, even in the absence of active gut inflammation.[46] Moreover, IBD-PSC patients have a distinct microbiota pattern, with an abundance of *Enterococcus*, *Streptococcus*, and *Veillonella* compared with IBD patients without PSC, which may be involved in the pathogenesis of PSC in IBD.[47–49]

The estimated prevalence of NAFLD is reported to be 25.2% worldwide, without significant differences between Western and Eastern countries.[50,51] It is noteworthy that NAFLD has been renamed as metabolic dysfunction-associated steatotic liver disease since 2023. The literature that directly related to our study all used the term "NAFLD," and there was no updated epidemiologic study that may affect the present results. The presence of NAFLD is associated with worse hospitalization outcomes in patients with IBD, and increased risk of liver cirrhosis and hepatocellular carcinoma.[52,53] We noted that IBD patients have a higher prevalence of NAFLD (26.1%–32%) than in the general population. Risk factors for the development of NAFLD in IBD patients include older age, obesity, metabolic disorders, longer disease duration, and prior surgery for IBD.[27–29] The genetic predisposition for NAFLD and IBD does not overlap, while inflammation plays a large role in both processes and represents a link between these two diseases.[54] In IBD patients, prolonged periods of disease and persistent intestinal inflammation increased the risk of NAFLD development. Dysbacteriosis plays a critical role in the pathogenesis of IBD and is

associated with disease severity.[55] Moreover, animal studies found that a high-fat diet can alter gut microbiota and predispose to hepatic steatosis,[56,57] suggesting dysbacteriosis may exert influence in the coexistence of IBD and NAFLD. Previous IBD-related enterectomy is also an important risk factor for developing NAFLD.[27,28] The reasonable mechanisms underlying this finding include small intestinal bacterial overgrowth, intestinal resection-associated metabolic syndrome, and systemic inflammation, which have been reported in the general population undergoing massive small bowel resection.[58,59] Comorbid NAFLD may affect treatment choices in IBD patients, as underlying liver steatosis could potentiate hepatotoxicity due to drugs. Immunomodulators, especially methotrexate, are closely associated with NAFLD in patients with IBD[28]; therefore, it might be better to avoid this drug in IBD-NAFLD patients. The data on the association between other treatment strategies (such as corticosteroids and biologics) and NAFLD in patients with IBD are limited and further clinical studies are needed for a more accurate conclusion.

The prevalence of gallstones in adults is up to 20% with considerable geographic variation, which is higher in Europe and the Americas than in Asia and Africa.[60,61] We found that the prevalence of gallstones in patients with IBD was reported to be 4.1%–12.4%, which appeared to be lower than in the general population. This was mainly due to a lack of well-controlled epidemiological studies and representative sample populations.[62] Notably, a meta-analysis with low heterogeneity and low publication bias demonstrated a trend toward higher prevalence of gallstone in patients with IBD, especially those with CD.[30] The most likely biological explanation for this is the impairment of enterohepatic circulation of bile acids in CD patients. After ileal resection or terminal ileum involved in CD patients may reduce absorption of bile acids, leading to the precipitation of cholesterol and gallstone formation.[63,64] Moreover, dysbiosis of intestinal flora in IBD patients may impair the metabolism of bile acids and conversion of primary bile acids to secondary bile acids, therefore increasing the incidence of gallstone.[65,66] In addition, the disordered gallbladder motility due to a prolonged fasting state, particularly in IBD patients on total parenteral nutrition (TPN), may promote biliary sludge and facilitate gallstone formation.[67] Importantly, more than 20% of newly developed gallstones in CD patients were symptomatic and required cholecystectomy,[62] suggesting that prevention strategies, such as ursodeoxycholic acid or stimulation of cholecystokinin secretion during TPN, could be considered in the management of CD subgroups at higher risk of gallstones.

Both acute and chronic pancreatitis are severe conditions that lead to hospitalization and possibly death. We noted that the risk of acute pancreatitis was increased in patients with IBD compared with non-IBD individuals, and this trend was more significant in CD patients.[33,34] Gallstone is regarded as one of the most common causes of acute pancreatitis. Thus, the higher prevalence of gallstones in patients with IBD, especially CD, might partly explain their association with the risk of acute pancreatitis. AIP is a rare disease with an estimated prevalence rate of 0.001%–0.004% in the general population.[68–70] We found that the prevalence of AIP in IBD patients was approximately 100-fold higher than in the general population. Immune-mediated pathways may be involved in the strong association between IBD and AIP. Autoantibodies against exocrine pancreatic tissue have been found in some patients with IBD.[71,72] In addition, a shared lymphocyte homing process occurs in the development of AIP and IBD.[73,74] The presence of IgG4-positive cells in colon tissues and elevated IgG4 serum levels in IBD patients also provided a possible link between AIP and IBD.[75,76] As the concurrence of AIP and IBD can worsen each clinical outcome, further studies are warranted to establish appropriate therapeutic strategies. The association between chronic pancreatitis and pancreatic exocrine insufficiency with IBD has also been reported,[77] but there is no eligible meta-analysis included in this umbrella review. Previous studies have shown that IBD medications were implicated in acute pancreatitis, including azathioprine, mercaptopurine, mesalazine, and sulfasalazine.[78,79] The risk of acute pancreatitis in drug exposure does not follow a dose-related pattern, and this effect is probably better classified as allergic or idiosyncratic.[79] Moreover, patients with CD seem to have a higher risk for azathioprine/mercaptopurine-induced acute pancreatitis.[79] In this umbrella review, we deliberately excluded studies on acute pancreatitis resulting only from drug treatment to avoid overestimating the contribution of IBD disease itself. A previous study systematically

reviewed the association between IBD and a wide spectrum of pancreatic diseases, showing a significantly increased risk of acute pancreatitis and AIP in patients with IBD and the risk factors were consistent with our findings.[80] Due to the high heterogeneity of included studies, no quantitative synthesis was possible in this systematic review. Here, we included only meta-analyses to obtain qualitative data, which allowed for a more precise estimation of the effect.

PVST is a potentially lethal extraintestinal manifestation in patients with IBD.[81,82] The prevalence of PVST was reported to be 0.12%–0.21% in IBD.[19,31] Patients with PVST frequently have esophageal or gastric varices, and the most common clinical presentation is gastrointestinal bleeding. PVST may also lead to intestinal ischemia and infarction if the clot extends into the superior mesenteric vein, further increasing the risk of mortality in IBD patients.[31] The impairment of the mucosal barrier in IBD may lead to microbial translocation to the portal venous system and subsequent pylephlebitis, increasing the risk of PVST.[11] IBD-associated coagulation abnormalities, including increased levels of coagulation factors V and VIII, platelet count, and fibrinogen, as well as deficiency of anti-coagulants also contribute to the development of thrombotic events, including PVST.[83–85] Notably, the incidence of PVST was increased in severe IBD patients who underwent corticosteroid therapy and colorectal surgery.[31] Imaging examinations such as CT or MRI should be considered in these high-risk patients to early detect PVST.[86]

AIH is an immune-mediated disease that may progress to decompensated cirrhosis and require a liver transplant.[87] We noted that the prevalence of AIH in IBD patients was more than 100-fold higher than in the general population.[19,39] AIH may also occur in the setting of overlap syndromes such as AIH-PSC and AIH-PBC.[88–90] Moreover, medications used for IBD, particularly tumor necrosis factor inhibitors, have been reported to induce or exacerbate AIH.[90] Some studies have shown that IBD patients with AIH were more likely to relapse and require surgery compared to IBD patients without AIH.[91,92] Therefore, it is important to early detect the coexistence of AIH and IBD to properly direct management. Immunosuppressive and immunomodulatory drugs used in IBD may not only increase the risk for HBV and HCV infection but also lead to HBV reactivation.[87,93,94] This will have more impact on Asian countries due to the high prevalence of HBV infection. Although the prevalence of markers of viral hepatitis was reported to be similar between IBD patients and the general population,[38] screening for chronic HBV and HCV is crucial before starting the immunosuppressive treatment in IBD.

Chronic inflammatory state in patients with IBD increases the risk for intestinal cancers, but the association with extraintestinal cancers is uncertain.[37] Treatment with immunosuppressants and biologics could impair the immune environment of IBD patients and weaken their host defense against tumors. An earlier umbrella review focused on the associations of IBD with overall and site-specific cancer risk and showed that CD patients had an increased risk of developing cholangiocarcinoma, hepatocarcinoma, and pancreatic cancer, while UC patients were more likely to develop bile duct cancer and pancreatic cancer.[95] In agreement with these previous studies, our findings demonstrated that patients with IBD had an increased risk of hepatobiliary and pancreatic malignancies, particularly cholangiocarcinoma.[35,36] These studies have low heterogeneity, providing relatively high-grade evidence. The increased risk of cholangiocarcinoma in patients with IBD is partly due to the high prevalence of PSC and gallstones.[95–97] NAFLD and AIH occur more frequently in patients with IBD and constitute a risk factor for hepatocellular carcinoma.[95]

There were limitations in this umbrella review. We included only associations assessed by systematic reviews and meta-analyses of observational studies, hence the associations not yet studied with these methods might be missed. It must be acknowledged that all included meta-analyses were of low or critically low quality by AMSTAR 2 rating. Assessing the quality of primary studies should be performed by authors of the original meta-analyses and is beyond the scope of an umbrella review. Even so, any heterogeneities and biases, or methodological flaws in the design or conduct of the original studies may affect the pooled estimates. Moreover, some associations presented in this study were derived from meta-analyses that included a limited number of original studies or did not provide the exact number of included subjects. This scenario could be attributed to the inherently low prevalence of the diseases, thereby increasing the risk

of publication bias. In addition, synthesizing data derived from observational studies that used the general population as the comparator group may lead to detection bias, for hepatobiliary and pancreatic diseases can be discovered more often and earlier in patients with IBD due to rigorous medical monitoring. Another limitation is the different diagnostic criteria used in the primary studies, influencing the disease classification and outcomes. Finally, although we assessed the strength of epidemiologic evidence according to robust, prespecified criteria and reported any evidence of biological plausibility, our findings rely mostly on meta-analyses of observational studies, therefore only association, rather than causation, can be established.

This systematic umbrella review demonstrated the significant associations between IBD and multiple hepatobiliary and pancreatic diseases, including PSC, NAFLD, gallstones, acute pancreatitis, AIH, AIP, PVST, and cholangiocarcinoma. Although the biological basis for some of these associations is not fully understood, there are convincing hints of biological plausibility for most of them. Given these manifestations can substantially impact the quality of life, our findings have clinical significance for screening, treatment, and management practices for IBD patients. The intensive surveillance and early detection of PSC, AIH, AIP, PVST, and cholangiocarcinoma in IBD patients is important to prevent their deleterious clinical course and improve the prognosis. Before starting treatment for IBD, screening for NAFLD, gallstones, HBV, and HCV is crucial to avoid therapy-related adverse events. Effective management of IBD-associated hepatobiliary and pancreatic diseases often requires a multidisciplinary team of gastroenterologists, hepatologists, and oncologists. In addition, patient education is important for early detection, treatment decisions, and regular follow-up of their conditions. Given the limitations of the current primary evidence, future high-quality prospective studies are warranted to substantiate these findings and identify IBD patients who are more at risk and would benefit the most from tailored screening programs.

Declarations

Ethics approval and consent to participate

This study was an umbrella review in which no human subject or animal was employed.

Consent for publication

Not applicable.

Author contributions

Runsheng Hong: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing – original draft.

Zhixue Li: Data curation; Formal analysis; Investigation.

Meng Li: Methodology; Resources; Supervision; Writing – review & editing.

Yun Dai: Conceptualization; Methodology; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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