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Systematic review—pancreatic involvement in inflammatory bowel disease

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Summary

Background: Inflammatory bowel disease (IBD) is a chronic inflammatory immune-mediated disorder of the gut with frequent extra-intestinal complications. Pancreatic involvement in IBD is not uncommon and comprises a heterogeneous group of conditions, including acute pancreatitis (AP), chronic pancreatitis (CP), autoimmune pancreatitis (AIP) and pancreatic exocrine insufficiency (PEI); however, data on such an association remain sparse and heterogeneous.

Method: PubMed/MEDLINE and EMBASE databases were searched for studies investigating pancreatic involvement in patients with IBD.

Results: Four thousand one hundred and twenty-one records were identified and 547 screened; finally, 124 studies were included in the review. AP is the most frequent pancreatic manifestation in IBD; the majority of AP cases in IBD are due to gallstones and drugs but cases of idiopathic AP are increasingly reported. AIP is a rare disease, but a strong association with IBD has been demonstrated, especially for type 2 and ulcerative colitis. The pathogenetic link between IBD and AIP remains unclear, but an immune-mediated pathway seems plausible. An association between CP and PEI with IBD has also been suggested, but data are to date scarce and conflicting.

Conclusion: This is the first systematic review of the association between IBD and pancreatic diseases. Gallstones and drugs should be considered the most probable causes of AP in IBD, with type 2 AIP also being possible.

The Handling Editor for this article was Dr Mike Burkitt, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory immune-mediated disorder of the gut. It is considered a multisystemic disorder since up to 50% of patients experience at least one extra-intestinal manifestation.[1] Extra-intestinal presentations may virtually involve any organ and system with a potentially detrimental impact on the patient's functional status and quality of life.

Pancreatic involvement is not uncommon but is often underestimated and neglected.

Several pancreatic conditions have been reported with increased prevalence in CD and UC compared to the general population.[2] Pancreatic abnormalities in IBD include acute pancreatitis (AP), chronic pancreatitis (CP), autoimmune pancreatitis (AIP), pancreatic exocrine insufficiency (PEI) and asymptomatic abnormalities, comprising both imaging and laboratory findings.[3] As for causality, the involvement of the pancreas in IBD may be framed in the autoimmune process itself or be iatrogenic.

We, therefore, aimed to investigate pancreatic involvement in patients with IBD by performing a systematic review with the objective to evaluate the aetiology, prevalence and impact of pancreatic diseases in patients with IBD.

2 | METHODS

2.1 | Data sources

This systematic review was performed and reviewed according to the updated Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) statement.[4] A computerised literature search was performed in PubMed/MEDLINE and EMBASE databases (from January 1970 to January 2022) to retrieve pertinent primary studies.

The search terms "Inflammatory bowel disease", "Crohn's Disease", "Ulcerative colitis" "Idiopathic acute pancreatitis", "drug-induced pancreatitis", "Autoimmune pancreatitis", "pancreatitis", "chronic pancreatitis", "hyperamylasemia", "Cholelithiasis", "exocrine pancreatic insufficiency", "Pancreatic ductal adenocarcinoma", "asymptomatic pancreatic abnormalities", "pancreatic diseases" with synonyms were combined. The search strategy included both medical subject headings (MeSH) terms and free language words.

Specific search terms were defined as detailed in Appendix S1. The titles of all identified articles were screened to evaluate their relevance, and the abstracts and/or full texts of selected potentially relevant papers were further evaluated. With a snowball method, additional articles were searched by hand-searching reference lists of all the articles retrieved to identify potentially relevant studies. Non-English language papers were excluded. The protocol of this systematic review has been submitted in the International Prospective Register of Systematic Reviews (PROSPERO, ID 314688) and is available on request from the corresponding author.

2.2 | Study selection criteria

Both retrospective and prospective studies, single-arm, cross-sectional (cohort or case–control), case-series and reports, registry-based studies, controlled and randomised studies were included. Editorials, reviews, systematic reviews, meta-analysis, preprint, conference abstracts, study register entries, clinical study reports, dissertations, unpublished manuscripts, government reports or any other document providing relevant information were also retrieved. The research included studies of patients with both CD and UC. Articles published as abstracts were included, whereas non-English language papers were excluded.

2.3 | Quality assessment of primary studies

All of the included studies were evaluated according to their methodological quality, study design (case-series and reports, single-arm, cross-sectional, registry-based studies, controlled and randomised studies), patient selection (consecutive or non-consecutive), data collection (prospective, retrospective or unknown), statistical methods, endpoints and length of follow-up. The quality of included studies was assessed according to Newcastle–Ottawa scale.[5]

2.4 | Methods of the review of the literature

Six reviewers (S.M., I.F., C.V., L.P., L.C. and M.F.) identified all the articles divided by topic (two reviewers by each topic). The reviewers screened all the articles based on the title article and abstract. Duplicates were identified and removed. The remaining studies were assessed by examining the full-text papers for adherence to the topic. The data concerning the types of participants and outcome measures were independently extracted by the reviewers, who openly discussed any discrepancies. Only in the case of disagreement was the further and definitive judgement of an independent clinical expert (G.C.) applied. The excluded studies and the reasons for exclusion were recorded.

2.5 | Ethics approval

Ethical approval was not required as data are not individualised, and primary data were not collected.

3 | RESULTS

A total number of 4121 studies were identified and 547 screened. After filtering for English language, human studies, year range, article type and removing duplicates, 202 full-text articles were considered. Out of these, 124 studies constituted the final dataset as containing pertinent data. Figure 1 represents the study selection process in the PRISMA 2020 diagram.[4]

Considering the clinical heterogeneity of all the studies, no quantitative synthesis was possible and the results of the review are presented and discussed being organised by topics.

3.1 | Acute pancreatitis

AP is the most frequent pancreatic disorder associated with IBD and it is characterised by acute inflammation of the pancreatic parenchyma. We identified 82 studies regarding AP in IBD (Figure 1), eight concerning 'epidemiology', 74 concerning 'aetiology', of which five regarding 'gallstone disease', 46 'drug-induced AP', two 'idiopathic AP', 21 'other causes'.

3.2 | Epidemiology

In the general population, the incidence rate of AP ranges from 10 to 44 per 100,000/year,[6] being one of the leading causes of hospital admission and expenses for digestive diseases.[7] Patients with IBD seem to be at increased risk for acute pancreatitis.

We identified eight studies specifically dealing with the epidemiology of AP in patients with IBD.[8–15] A population-based cohort study in Taiwan reported the overall incidence of AP in IBD to be 3.56-fold higher than in patients without IBD.[8] In a retrospective study by Bermejo et al. 82 episodes of AP were observed in 67 patients (53 CD and 14 UC), in a total of 5073 IBD patients, with a cumulative incidence of AP in IBD of 1.6% during a mean follow-up period of 14 years.[9] Similarly, in a study of 852 patients with CD, the incidence rate of AP was 1.4%, over a follow-up period of 10 years.[10] A Danish 16-year nationwide follow-up study demonstrated an elevated risk of AP with an incidence rate of 4.3% and 2.1%, in CD and UC respectively.[11] Moreover, in a recent retrospective cohort study conducted at nine Spanish IBD referral centres, 185 patients with IBD (68.7% CD) were identified with a first episode of AP, between 1998 and 2018.[12] A retrospective study analysing paediatric and adult patients presenting with AP as the first symptom of IBD demonstrated that AP preceded the diagnosis of IBD in 2.17% (10/460) of paediatric patients with IBD, compared to only 0.06% (2/3500) of adult patients with IBD.[13]

In a recent meta-analysis, the risk of AP was increased in patients with IBD and particularly higher in patients with CD. The overall estimated risk ratio for AP was 2.78 in patients with IBD and 3.62 and 2.24 for CD and UC respectively. Due to the observational design of the studies included, the mechanisms underlying the increased risk of pancreatitis are unknown and remain to be investigated.[14]

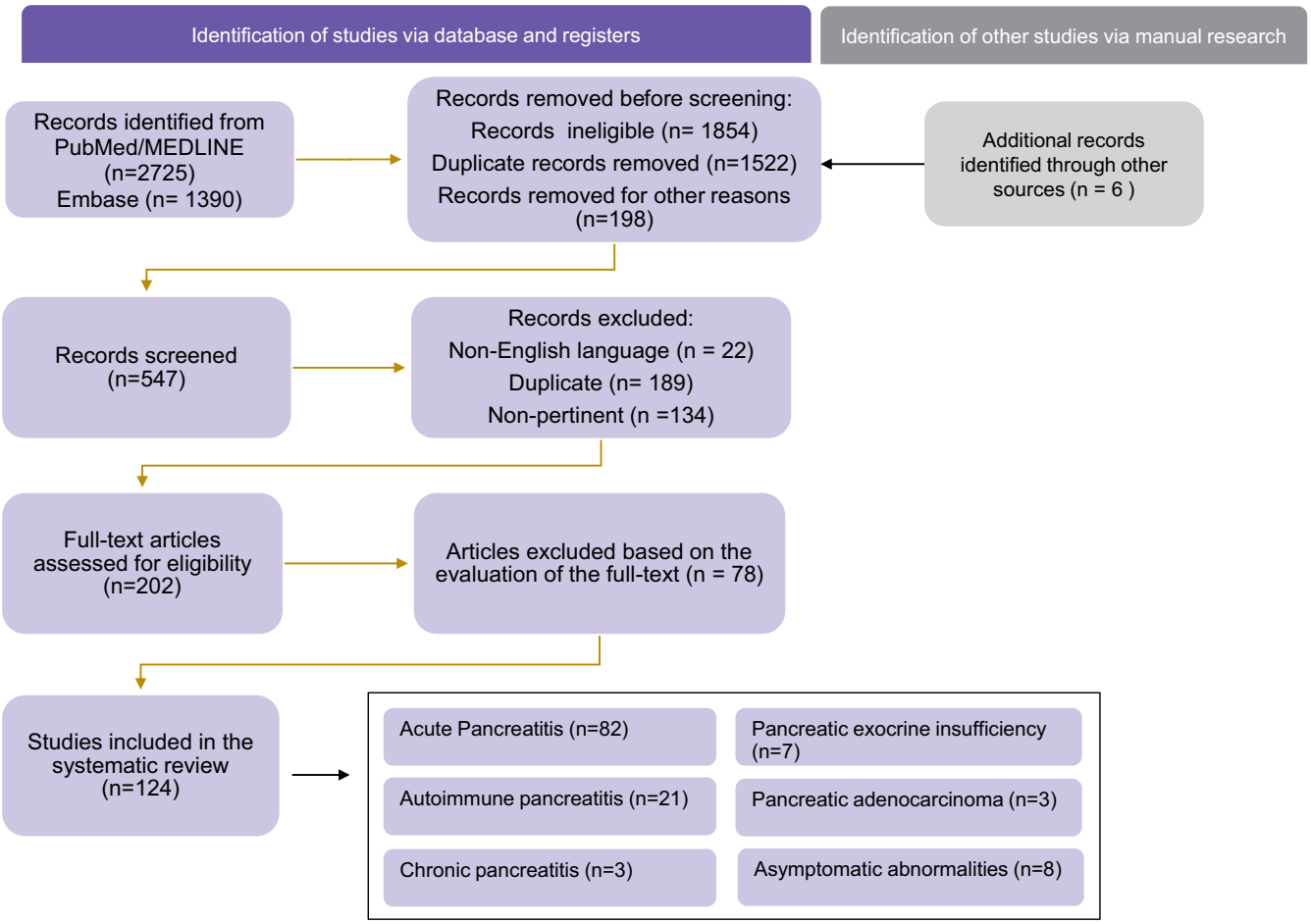

FIGURE 1 PRISMA 2020 diagram showing the study selection process, with the results divided by topics

Another meta-analysis confirmed that IBD elevates the risk of AP with a pooled annual incidence of AP in IBD of 210/100,000 person-years (95% CI, 84–392/100,000 person-years).[15]

While not all of these studies clearly defined AP following the revised Atlanta classification of AP,[16] in the large majority of them the diagnosis was made on clinical basis; therefore, asymptomatic cases of hyperamylasaemia/lipasemia alone should not affect the results. Moreover, the results of these studies and the two retrieved meta-analyses, uniformly document a significantly increased risk of AP in patients with IBD.

3.3 | Aetiology

A wide variety of factors may cause AP in IBD (Table 1), including gallstones, adverse effects of drugs, duodenal inflammatory lesions, iatrogenic harm accompanying endoscopic procedures, primary sclerosing cholangitis (PSC) and autoimmunity. Not infrequently, a precise cause cannot be identified, thus defining also a group of idiopathic AP (IAP).[12]

3.3.1 | Cholelithiasis

Cholelithiasis is one of the most common causes of AP in IBD and a strong association between gallstones formation and CD has been demonstrated.

We identified five studies dealing with the association between IBD and gallstone disease.[17–21] According to a meta-analysis specifically investigating this association, patients with IBD had a significantly higher prevalence of gallstones compared to the control group [odds ratio (OR) 1.72, 95% confidence interval (CI) 1.40–2.12, P < 0.0001]; the subgroup analyses showed that the risk of cholelithiasis was increased in CD patients (OR 2.05, 95% CI 1.61–2.63, $P < 0.0001$) but not in UC patients (OR 1.12, 95% CI 0.75–1.68, $P = 0.585$).[17] Many independent factors in CD have been related to gallstones development, namely site of disease at diagnosis (ileocolonic location), lifetime surgery, the extent of ileal resections (>30 cm), number of clinical recurrences (>3), total parenteral nutrition and frequency and duration of hospitalisations.[18,19] Indeed gallstones development is mainly due to the malabsorption of bile salts in the ileum, which leads to impaired enterohepatic circulation.[20] Also, total parenteral nutrition and a prolonged fasting state may reduce gallbladder emptying, and this may further increase the risk of the development of gallstones and biliary sludge.[18,21]

TABLE 1 Causes of acute pancreatitis in inflammatory bowel disease (IBD)

Cholelithiasis
Drug-induced
Higher Likelihood of association
Azathioprine (AZA) and its active metabolite 6-mercaptopurine
Salazopyrine and 5-ASA-derived drugs
Antibacterial agents (Metronidazole)
Lower Likelihood of association
Corticosteroids
Biological agents (infliximab and vedolizumab)
Autoimmune pancreatitis (AIP) (Type 2)
Idiopathic acute pancreatitis (IAP)
Duodenal inflammatory lesions (stenosis, fistula, direct infiltration of inflammation)
Post-procedural (small bowel endoscopy)
Primary sclerosing cholangitis (PSC)

3.3.2 | Drug-induced acute pancreatitis

Many drugs used to treat IBD are potentially pancreato-toxic and drug-induced AP is particularly frequent in the IBD population.[2,22–24]

The occurrence of AP due to thiopurines, namely azathioprine (AZA) and its active metabolite 6-mercaptopurine has been described since the 1970s.[9,25–31] Since then, at least 16 studies explored this topic and were included in this systematic review.[9,25–39]

This side effect is reported in up to 7.3% of patients with IBD taking AZA in longitudinal prospective and retrospective studies,[27,28] while in a recent meta-analysis focusing on AZA and 6-mercaptopurine for maintenance of remission in ulcerative colitis a lower frequency, below 3%, was reported.[32] However, this meta-analysis was not focused on drug-induced AP, so it may underestimate its frequency; moreover, it seems that the incidence is higher in patients with CD compared to UC; the female gender is also associated with a 3.4-fold higher risk and smoking seems to be the strongest risk factor for thiopurine-induced AP.[33] It is a likely idiosyncratic, dose-independent and unpredictable adverse drug reaction, usually occurring in the first month of therapy.[33] The course of thiopurine-induced AP is usually mild with rapid clinical improvement on withdrawal of the offending drug. In a prospective study, 24% presented nausea and vomiting, and 14% had fever, 43% of patients required hospitalisation with a median inpatient period of 5 days; only 10% of patients developed peripancreatic fluid collections, yet none required surgical/endoscopic intervention.[28] In a recent retrospective study on 787 IBD patients on AZA, the rate of abdominal pain was 6.9%, but only 3.3% of patients had AP, typically within the first 2 months of treatment, with active smoking being the only independent risk factor for AZA-induced AP (OR = 3.2).[34]

Many pathophysiological mechanisms have been proposed, including immunologic reactions and direct toxic effects. Genetic polymorphisms have been strongly associated with the development of thiopurine-induced pancreatitis: a genome-wide association study (GWAS) identified a strong association between the Class II HLA gene region polymorphism (rs2647087) and thiopurine-induced AP,[35] with the estimated risk being 9% in patients heterozygous at rs2647087 and 17% in homozygotes.[36] On the other hand, polymorphisms in the thiopurine S-methyltransferase (TMPT) gene,

which are known to be associated with other dose-independent side effects, such as hepatotoxicity and myelotoxicity, showed no association with thiopurine-induced pancreatitis.[37]

Wilson and colleagues screened their patients with IBD who were candidates for treatment with AZA for the haplotype HLADQA1-HLADRB1*07:01A > C haplotype that has been associated with increased risk of AP after AZA and obtained an 11-fold reduction of this adverse event, suggesting that a personalised treatment strategy may reduce the risk.[38] Furthermore, in a more recent retrospective series, azathioprine-induced AP in patients with IBD was associated with AB0 blood group B (OR 3.17), which is an established risk factor for AP in general; this remained significant even after adjustment for known risk factors such as CD and active smoking.[39]

However, apart from these genetic analyses, it is often unpredictable which individuals are at risk for thiopurines-induced AP in clinical practice. Even other drugs could contribute to or precipitate AZA toxicity such as budesonide which has been reported as a risk factor of azathioprine-induced pancreatitis.[34] In very selected cases with mild pancreatitis, a re-challenge test has been attempted,[38] although the availability of many other treatments has rendered this approach unnecessarily risky.

5-ASA compounds, including sulphasalazine, mesalazine and olsalazine, have been less frequently involved in drug-induced AP. Ten of the selected studies addressed this association.[40–49]

AP as an adverse reaction to 5-ASA derivatives has been first described by Block et al,[40] and subsequently by several other authors,[41] although reports are sometimes conflicting.[42] It is reported to occur more frequently with mesalazine (7.5 per million prescriptions) compared to sulphasalazine (1.1 per million prescriptions) (OR 7.0; 95% CI 2.6–18.6; $p < 0.001$).[43] AP has been reported also with olsalazine[44] and even as a consequence of rectal 5-ASA enema administration.[45] A retrospective case–control study demonstrated that the risk of AP does not differ among patients using the mesalazine Multi Matrix System (MMX) or a comparator.[46]

The incidence has been estimated to be 1/million days of treatment.[49] However, the frequency of AP with the above medications is not clear and may be underestimated, as most evidence comes from case reports,[40,44–48] narrative reviews,[2,49] another systematic review, which collected 42 patients.[41] Only one population-based case–control study[42] evaluated 1590 incident cases of AP from the Hospital Discharge Registry of the North Jutland County of Denmark from 1991 to 2002 and among them, 21 patients had IBD and 5 were taking 5-ASA compounds. Most cases of 5-ASA-related AP occurred within the first 6 weeks of therapy, even if it can occur at any time point.[47] The course is mild, although rare cases of severe necrotising pancreatitis have been reported.[48] Clinical improvement usually occurs within 4 days after drug withdrawal.[47,49]

Regarding biological agents, nine studies were selected.[50–58] Drug-induced AP is an extremely rare adverse effect of biological agents with only a few cases reported for infliximab[50] and vedolizumab.[51] On the other hand, anti-TNF agents were also used to improve AP course in animal studies,[52–54] whether they may be of benefit in humans is unknown.

Multiple mechanisms have been hypothesised in the causative process of drug-induced pancreatitis, including pancreatic duct constriction, arteriolar thrombosis and an immune-mediated mechanism (similar to what was reported for hepatitis)[55,56]; tofacitinib, and to a lesser extent, infliximab are also known to cause lipid profile abnormalities, which theoretically could lead to hypertriglyceridemia-induced pancreatitis.[57,58]

Other medications could be involved in drug-induced AP in IBD. Antibacterials, such as metronidazole, are commonly employed as primary therapy for perianal Crohn's disease, with few reports of drug-induced AP.[59] A recent epidemiological study showed an increased risk of AP within 1 month of exposure to a single or combined regimen of oral metronidazole; however, a direct causality link, as well as the possible pathogenetic mechanism were not so clear.[60] It has been hypothesised that metronidazole may promote the formation of hydrogen peroxide, superoxide and other free radicals, which are toxic for pancreatic β-cells; other suggested mechanisms include immune-mediated inflammatory response and pancreatic duct constriction.[61]

AP has also been reported in association with steroids, as an extremely rare and debatable side effect.[62–65] One case–control study found a nearly threefold increased risk of AP in patients taking betamethasone and slightly lower for those taking prednisolone.[63] A recent meta-analysis, in the setting of systemic lupus erythematosus, reported a cumulative incidence of 5% of corticosteroid-associated AP,[64] with the risk reaching its highest level in the first 2–14 days after steroid administration and gradually decreasing thereafter.[62–64] On the other hand, another study in the setting of optic neuritis[65] did not show any increased risk.

To sum up, thiopurines, 5-aminosalicylic acid (5-ASA) compounds, and metronidazole are considered class Ia drugs, for which there is convincing evidence for the association with AP.[66] Indeed, they are among the drugs most commonly associated with drug-induced AP.[67] The evidence for an association with corticosteroids, and biological agents is weaker, the latter being exclusively based on case reports. At any rate, reports of drug-induced AP are often hampered by a lack of exclusion of all other possible causes and it has to be taken into account that, especially in older studies, the definition of AP was not standardised and an AP diagnosis may have been reported merely based on the elevation of pancreatic enzymes and abdominal pain (that may occur for many other reasons in patients with IBD), without radiological confirmation.

3.3.3 | Idiopathic acute pancreatitis

Cases of idiopathic acute pancreatitis (IAP) are increasingly reported both as initial presentation and as extra-intestinal manifestations in the course of IBD, without specific aetiological factors being documented. The present systematic review retrieved two studies.[12,68] According to a recent publication, IAP represents the second cause of AP in patients with IBD.[12] Among 185 patients with IBD (68.7% CD) and a first episode of AP, 38 (20.6%) fulfilled the criteria for IAP.

TABLE 2 Main features of type 1 and type 2 autoimmune pancreatitis (AIP)

	Type 1 AIP	Type 2 AIP
Median age at onset (years)	60	45
Sex difference	M > F	M = F
Clinical onset	Jaundice	Acute Pancreatitis
IgG–IgG4 elevated	Yes	No
Autoantibodies positive	Yes	No
Pancreatic histology	Lymphoplasmacytic sclerosing pancreatitis	Granulocytic epithelial lesion
Other organs involvement	IgG4 systemic disease Sclerosing cholangitis, sialadenitis. Retroperitoneal fibrosis	IBD (UC > CD)
Diagnostic elements[a]	Elevated IgG4 suggestive, Histology not mandatory	Concomitant IBD suggestive, Histology mandatory
Treatment strategy	Steroids	Steroids (IBD-therapy)
Recurrence risk	High (40%–60%) Maintenance therapy	Low (9%–25%) No maintenance therapy

[a]According to ICDC.

Differently from other causes of AP, IAP seemed more frequent in UC, with a mild course but with a high risk of recurrence.[12] In the same study, IAP patients also presented a significantly higher 5-year risk of developing chronic pancreatitis (5.2%).[12] Moreover, the 5-year risk of being diagnosed with autoimmune pancreatitis was higher in IAP patients (14.1% vs. 0.7%, log-rank $p < 0.001$). Finally, the course of IBD during the year that followed the first episode of IAP did not differ from the groups without IAP.[12] Therefore, in this category of patients, there are some cases of undiagnosed autoimmune pancreatitis type 2 and probably overlapping cases with drug-induced acute pancreatitis.

3.3.4 | Other causes

Several studies retrieved in the present systematic review reported other possible causes of AP, represented by duodenal and/or papillary lesions, procedural accidents due to either endoscopic balloons, or endoscopic retrograde cholangiopancreatography (ERCP), and primary sclerosing cholangitis (PSC).[69–89]

In duodenal manifestations of CD, it has been reported that, even rarely, fistulas in the duodenal papilla,[71] as well as stenosis of the duodenum[72] can cause reflux pancreatitis; even cases of direct inflammatory infiltration from the duodenum into the pancreas have been described.[73]

Small bowel enteroscopy (either single-balloon or double-balloon) is an endoscopic procedure that enables direct visualisation and histological sampling of the small bowel mucosa and is therefore useful in CD diagnosis and management.[74] Isolated post-procedure hyperamylasaemia, without pancreatitis, has been reported in 17–75% of patients who underwent peroral double-balloon enteroscopy (DBE)[75–77]; whereas post-procedural AP was reported in 0.7%–3.2% of cases.[75,76] In a prospective trial involving 48 patients undergoing peroral DBE, hyperamylasaemia, and hyperlipasemia after peroral DBE occurred in 12 of 48 patients (25%), whereas the incidence of AP was reported to be 12.5% when clinically diagnosed.[16] On the other hand, in another paper post-small bowel enteroscopy hyperamylasaemia was reported in 13 patients (16%), but none had complaints suggesting acute pancreatitis.[75] Total insertion length, duration and time between the first and second inflations of the balloon were risk factors for AP.[78] No differences were observed between single and double balloon endoscopies in a randomised multicentre trial including 130 patients[79] as well as in two recent meta-analyses.[80,81] Aetiology has not been defined yet, but the most likely mechanism seems to be related to vascular distress causing a hypoxic state, as supported by the experimental evidence of hypoxic areas and necrotic zones in the pancreatic tissue of pigs.[82]

PSC is an idiopathic disease in which multiple diffuse stenoses in the intrahepatic and extrahepatic bile ducts lead to progressive cholestasis.[83] The incidence and prevalence rates of PSC are not negligible in the United States and Northern Europe, with a reported incidence of 0.4–1.22 per 100,000 inhabitants/year and a prevalence of 4.15–16.2 per 100,000 inhabitants.[84] Both genetic and environmental factors are reported to be involved in its onset. It is a condition strongly associated with IBD: in the West 50–80% of patients with PSC develop complicating IBD, and common disease susceptibility genes with IBD have been found.[85] The association is stronger for UC than CD.[86] Although the exact mechanism remains unknown, it has been reported that PSC patients may develop AP.[87,88] It may be caused by the bile and sludge reflux into the pancreatic duct, possibly due to strictures of the distal part of the common bile and/or pancreatic ducts. Indeed, endoscopic biliary stent placement was reported to be effective to prevent recurrent pancreatitis.[87] Furthermore, PSC has been reported to be an independent risk factor for post-ERCP pancreatitis.[89]

3.4 | Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a chronic benign pancreatic disorder characterised by painless obstructive jaundice (with or without

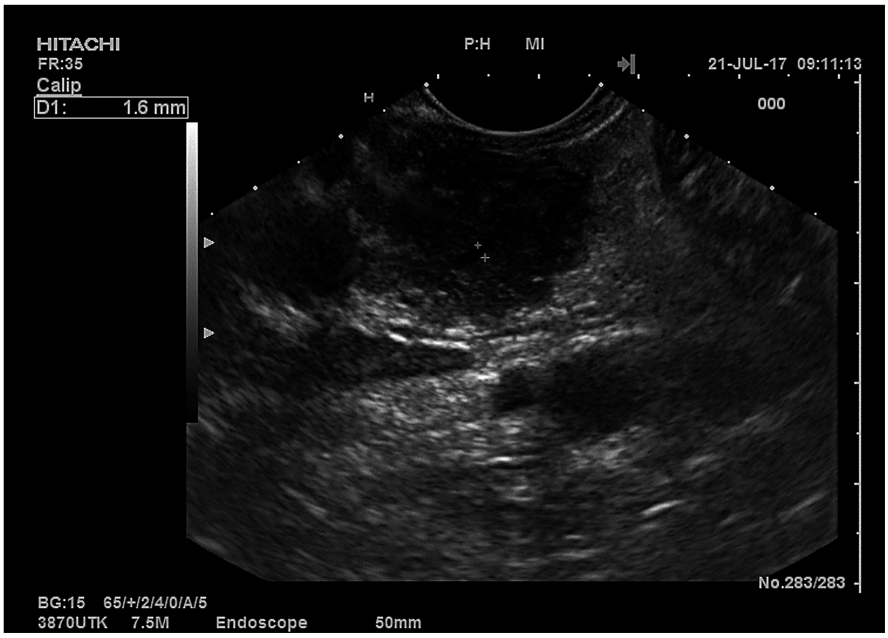

FIGURE 2 Endoscopic ultrasound appearance of autoimmune pancreatitis (AIP). The image shows the head of the pancreas examined from the duodenum with a diffuse coarse and hypoechoic appearance (sausage-shaped) in a patient with type 2 AIP. The main pancreatic duct was normal (calliper 1.6 mm)

a pancreatic mass), evidence of peculiar histology pattern of lymphoplasmacytic infiltrate and fibrosis, and a dramatic response to steroids.[90] Two distinct subtypes of AIP have been identified and specific diagnostic criteria have been detailed for both, assessing five main features, which are shown in Table 2.

Twenty-one studies on AIP in IBD were analysed in this systematic review[91–111] (Figure 1). AIP occurring in association with IBD is rather rare, yet the prevalence in IBD seems to be significantly higher than in the general population and, usually, it is of type 2.[91,92] AIP, especially type 2, appears to be more frequent in Western countries, with an estimated prevalence rate of 4.6–6% among acute and chronic pancreatitis cases and around 0.001–0.004% in the general population.[93–95] Only two studies conducted in Asia examined the prevalence of AIP in patients with IBD, reporting a prevalence of 0.3–0.5%,[96,97] which is approximately 100-fold higher than in the general population.[94,95] However, this rate may be underestimated, as suggested by studies demonstrating a frequency of pancreatic duct abnormalities in up to 10% of patients with IBD[112] and considering that type 2 AIP more often requires a challenging histological confirmation of diagnosis.

On the other hand, the prevalence of IBD in AIP patients has been reported to be 12–15-fold higher than in the general population[97,99,100]: an international multicentre survey found a prevalence of 16% UC and 1% CD among 64 patients with type 2 AIP, while IBD prevalence in type 1 AIP was much lower (1% among 153 patients).[101] As for isolated AIP, the prevalence of concomitant IBD-AIP varies widely worldwide, being less frequent in Asian Countries. In Western countries, the reported prevalence of UC among AIP patients was 30%–35%,[102] while studies from Korea and Japan reported a UC prevalence of 5.8% and 16% respectively.[96,97] Overall, there is an increased prevalence of AIP occurring in UC than in CD patients, since more than 60% of patients with concomitant IBD-AIP are affected by UC.[103]

IBD diagnosis usually precedes AIP diagnosis by 2–5 years[103] and a cumulative increasing probability of AIP after UC diagnosis has been reported (0.2% after 1 year, 0.8% after 10 years).[96,97] Yet, AIP can be the first manifestation of or even precede IBD in 25% and 20% of patients respectively.[103] In patients with pre-existing IBD, at the time of AIP diagnosis, most patients had active intestinal disease.[96,103] The mean age at AIP onset is 35 years and no gender predominance has been reported.[103]

The clinical presentation of AIP in IBD is rather similar to that of the isolated disease. Acute pancreatitis is the most common clinical presentation, up to 80% of patients in the largest series of AIP-IBD. In 15% of cases, associated inflammatory cholangitis was observed, which on the contrary is more common in type 1 AIP.[103]

The impact of AIP on the natural history of IBD has not been clearly defined yet, as available data are discordant. According to some authors, IBD associated with AIP carries a worse prognosis compared to IBD alone, with a higher proportion of extensive colitis and increased risk of colectomy reported both for UC and CD.[97,99] Other studies, however, found no differences in UC extent or activity in patients with or without AIP.[96] Interestingly, in the largest multicentric retrospective series published to date, comprising 91 patients with AIP-IBD, in UC patients, AIP was independently associated with a history of colectomy (OR, 7.1; 95% CI, 2.5–20, $P<0.05$) but also with rectal location (OR, 2.9; 95% CI, 1.3–6.3; $P<0.05$). One may infer that two different groups of UC patients seem at the highest risk of AIP: a) patients with extensive and refractory UC, carrying a higher risk of colectomy, and b) patients with mild distal location.[103] In the same series, CD-AIP patients had less stricturing–penetrating behaviour, including less perianal disease and again a higher risk of colectomy.[103]

The typical imaging finding of AIP, especially of type II disease, is a diffuse pancreatic enlargement, which gives the gland a sausage-shaped appearance, in some cases with a low-attenuating capsule-like rim[90,91] (Figure 2), associated with main pancreatic duct (MPD)

diffuse or focal stricture with possible upstream dilatation. However, AIP (more frequently type I) may also present as focal and subtle changes; in this case, the diagnosis is challenging and the possibility of malignancy has to be ruled out.

The pathogenetic link which correlates IBD and AIP is still unclear, but an immune-mediated pathway seems reasonable. In the largest series published to date, at the time of AIP diagnosis, more than 70% of patients had an active intestinal disease, thus suggesting a role for systemic inflammation in the pathogenesis of AIP.[103] A shared lymphocyte homing mechanism has been proposed: it has been reported that in AIP marked lymphoid infiltration produces tertiary lymphoid tissues, that resemble gut-associated lymphoid tissue (GALT) with over-expression of mucosal addressin cell adhesion molecule 1 (MadCAM-1) and peripheral lymph node addressins, as observed in active UC.[104] Indeed, from a histological point of view, type 2 AIP diagnostic characteristic is the granulocyte epithelial lesion caused by neutrophil infiltration of pancreatic duct epithelium[105–107] which resembles the crypt abscesses observed in the colonic mucosa of patients with UC.[106,108]

On the other hand, a possible link between IBD and type 1 AIP has also been hypothesised, as part of an IgG4 systemic disease and in a study by Ravi et al. patients with a previous diagnosis of UC were reported to have an increased number of IgG4-positive cells (10/HPF) on colon samples.[99] Yet, other authors also found that up to 4% of patients with IBD had elevated IgG4 serum levels with the possible diagnosis of IgG4-related systemic disease, even if none of them had evidence of autoimmune pancreatitis.[109]

For what concerns treatment, both type 1 and 2 AIP show a dramatic response to steroid therapy; high dose prednisolone (0.6 or 40 mg/day) for 4 weeks is the recommended treatment, then gradually tapered by decrements of 5 mg over 2–3 months.[91] Relapse rates are significantly higher in type 1 AIP patients, ranging between 40 and 60% compared with 9–25% in type 2 AIP.[93,110] Treatment response and recurrence rate in AIP-IBD patients seem to be similar to type 2 isolated AIP. In the largest published cohort, 34% of patients had at least one recurrence, whereas 20% had steroid-dependent AIP, which was successfully treated with azathioprine in the majority of them.[103]

Nowadays, although many patients with concomitant AIP-IBD may already be receiving immunomodulators or biologics at AIP diagnosis, published data on the effect of these drugs on type 2 AIP are still lacking and steroid therapy continues to be the mainstay of AIP treatment.

Recently, successful treatment of type 2 AIP with colchicine has been reported, with its rationale based on its inhibitory effect on neutrophils, the most characteristic immune cells infiltrating type 2 AIP.[111]

3.5 | Chronic pancreatitis

Chronic pancreatitis (CP) is a chronic inflammatory and fibrotic disease leading to progressive loss of exocrine (acinar cells) and endocrine (islets) tissue.[113] CP can be a result of recurrent flares of AP, especially when the aetiological factors, such as smoking, alcohol consumption, are not treated. CP is usually diagnosed based on clinical features: chronic or relapsing pancreatic-type pain (epigastric pain radiating to the back), even if there is currently no diagnostic reference standard; thus the combination of clinical signs, diagnostic imaging findings usually lead to the diagnosis of CP.

An association between IBD and CP has also been suggested in at least three studies, included in this systematic review[98,114,115]; however, high-quality studies are lacking, therefore evidence remains limited,[69] and further studies are warranted.[14]

A multicentric French study, conducted between 1981 and 1996, retrieved six patients presenting with features of idiopathic CP and UC and two patients with concomitant CP and Crohn's disease; a review of the literature performed in the same paper identified six additional cases of CP associated with UC and 14 associated with Crohn's disease.[98] In the same study, CP was associated with extensive disease and the risk of total colectomy in UC, suggesting a correlation between disease severity and progression.[98] Moreover, weight loss and pancreatic duct stenosis were also more frequent in UC compared to Crohn's disease (41% vs 12% and 50% vs 23% respectively).[98] Pathological specimens were analysed in five patients and demonstrated the presence of inter- and intra-lobular fibrosis with marked acinar regression in three and the presence of granulomas in two patients, both with Crohn's disease.[98] A recent nationwide population-based cohort study in Taiwan demonstrated that the incidence of CP in patients with IBD was 10.3 higher than that in non-IBD patients (5.75 vs 0.56 per 10,000 person-year). On the other hand, the CP cohort exhibited a higher risk of developing IBD, with a significantly higher risk for Crohn's disease (adjusted hazard ratio = 12.9) as compared to UC (adjusted hazard ratio = 2.80).[115] There are several possible aetiological factors for CP in IBD. AIP can progress to CP and may justify at least some of these cases. Recurrent AP episodes caused by drugs or other causes may also result in CP. Also, environmental factors associated with Crohn's disease such as smoking also cause CP.[69,113] In patients with IBD, CP symptoms, such as abdominal pain or steatorrhoea, may actually worsen IBD-related symptoms, further reducing the quality of life. CP pain is, unfortunately, difficult to manage, often requiring a multidisciplinary approach with a pain management team.[113]

3.6 | Pancreatic exocrine insufficiency

Pancreatic exocrine insufficiency (PEI) refers to the presence of maldigestion and malabsorption of nutrients as a consequence of a severely reduced pancreatic enzyme output, usually less than 10% of that necessary to sustain normal digestion.[116]

Data regarding PEI during the course of IBD are scarce and conflicting. We identified seven studies addressing this topic.[117–123] In an Italian cross-sectional study, PEI was frequently demonstrated in patients with IBD, when screened by the faecal

elastase-1 test and, in this study, using a cut-off of ≤200 μg/g, PEI was found in 22% of UC and 14% of CD patients, with an overall OR for patients with IBD of 10.5 compared to controls. The risk of PEI was related to loose stools, a larger number of bowel movements per day, and previous surgery[117]; PEI was reversible in most patients and persistent PEI was not associated with clinically active disease.[117] Possible mechanisms for the development of PEI in CD include pancreatic autoantibodies, duodenal reflux or duodenal–pancreatic anatomical alterations,[118] and reduced hormone secretion from the gut resulting in reduced stimulation of pancreatic juice.[119] The presence of pancreatic autoantibodies directed against the exocrine portion of the pancreas has been reported in about one-third of CD patients.[120,121] However, the association between CD and PEI is not fully elucidated. A recent study failed to demonstrate a substantial association between PEI and CD, using the faecal elastase-1 test.[122] As regards UC, data are even more limited.[123] A critical point is the diagnostic method used to diagnose PEI. Among indirect pancreatic function tests, faecal elastase-1 is the most commonly employed.[124] It is commonly accepted that a faecal elastase-1 level ≤200 μg/g stool indicates PEI, with levels of 100–200 μg/g typically indicating mild to moderate impairment and levels <100 μg/g reflecting severe impairment.[125,126] However, faecal elastase test has limitations as a definitive reference standard for PEI diagnosis[127] and poor diagnostic accuracy has been reported in patients with diarrhoea as dilution can lead to false-positive results.[128] This should be considered carefully in patients with active IBD.

3.7 | Pancreatic ductal adenocarcinoma

Data regarding the risk factors of hepato-pancreato-biliary neoplasms in IBD patients with or without PSC are scanty and conflicting. Three large studies were selected.[70,129,130] In a large Korean study, evaluating 5595 CD and 10,049 UC from 2011 to 2014 to explore the overall cancer risk in patients with IBD, a significantly increased PDAC risk (OR 8.6, 95% CI 1.0–31.0) was reported only in women with CD.[129] In another multicentric cohort study, including 5506 patients with CD and 5522 patients with UC (of whom 2% were affected by PSC), an association with neoplastic lesions was related to concomitant PSC.[70] In this study, the incidence of PDAC was higher (OR 11.22, 95% CI 4.11–30.62) in patients with IBD and PSC compared to patients with IBD and without PSC.[70] More recently, in a population-based cohort study from Norway and Sweden, among the 141,960 IBD patients (3.2% with PSC), 282 pancreatic cancers were diagnosed, during a median follow-up of 10.0 years (standardised incidence ratio 1.3, 95% CI 1.2–1.5). The relative risk of PDAC was considerably higher in PSC-IBD patients, with a standardised incidence ratio of 9.0; however, the standardised incidence ratio was still slightly increased also in non-PSC-IBD patients, compared to the general population.[130]

Several hypotheses have been made on the etiopathogenetic mechanisms underlying this possible association between IBD and PDAC. The immunosuppressive treatment, used to control disease activity, might have a role by impairing immune surveillance; another possible hypothesis is that chronic inflammation (particularly in the context of PSC) could be associated with an increased risk of cancer.[70] Environmental factors associated both with the risk of PDAC and CD such as smoking may also contribute to the association.

However, a clear association has not yet been demonstrated, and further studies are needed.

3.8 | Asymptomatic abnormalities

Asymptomatic hyperamylasaemia or hyperlipasemia and abnormalities of pancreas morphology have been reported in variable percentages in IBD. We reviewed five studies facing this topic.[131–135]

Elevation of serum pancreatic enzymes, in the absence of any clinical symptoms and morphological alteration, has been demonstrated in 11%–14% of patients with IBD after excluding other possible causes, such as renal impairment, familial pancreatic hyperenzymemia, macroamylasemia and salivary gland disease.[131,132,134] The prevalence seems to be slightly higher in UC compared to CD (11 vs 7% respectively) and in patients with concomitant PSC.[134] However, clinical relevance and association with IBD remain unclear and even if these abnormalities are relatively common in IBD, they are usually harmless, and even their role in the development of exocrine pancreatic insufficiency has not been confirmed.[112,133] Therefore, the measurement of lipase and amylase should be avoided in patients with IBD and without evidence of AP, as lipase and amylase are only of diagnostic value in AP, but not in any other pancreatic disease.

A possible cause of hyperenzymemia is the presence of pancreatic antibodies, found in up to 39% of CD patients compared with 4%–23% of UC patients and 3% of healthy controls,[135] and directed against exocrine pancreas, glycoprotein 2 and CUB/zona pellucida-like domain-containing protein (CUZD1) antigens. They seem to correlate with CD location and behaviour, being more prevalent in the case of ileitis and previous surgical intervention,[136] stricturing behaviour and perianal disease[137] and in case of early IBD onset (age at diagnosis ≤16 years).[138] However, none of these appears to be specific and they have been found in many other autoimmune diseases,[139] such as refractory celiac disease, PSC without IBD and patients with cholangiocarcinoma.[140,141] Finally, also some asymptomatic radiological abnormalities are described. We found three studies addressing radiological abnormalities.[112,123,142]

In a radiological study with magnetic resonance cholangiopancreatography (MRCP), pancreatic abnormalities of the ductal system have been reported in 16.4% of asymptomatic UC patients with no history of alcohol intake or previous episodes of acute pancreatitis. Such abnormalities seem to be more prevalent in patients with concomitant PSC.[123,142] A more recent study showed a rate of pancreatic duct abnormalities of 10.8% in patients with IBD; however, no distinction has been reported regarding patients with a previous history of pancreatitis.[112]

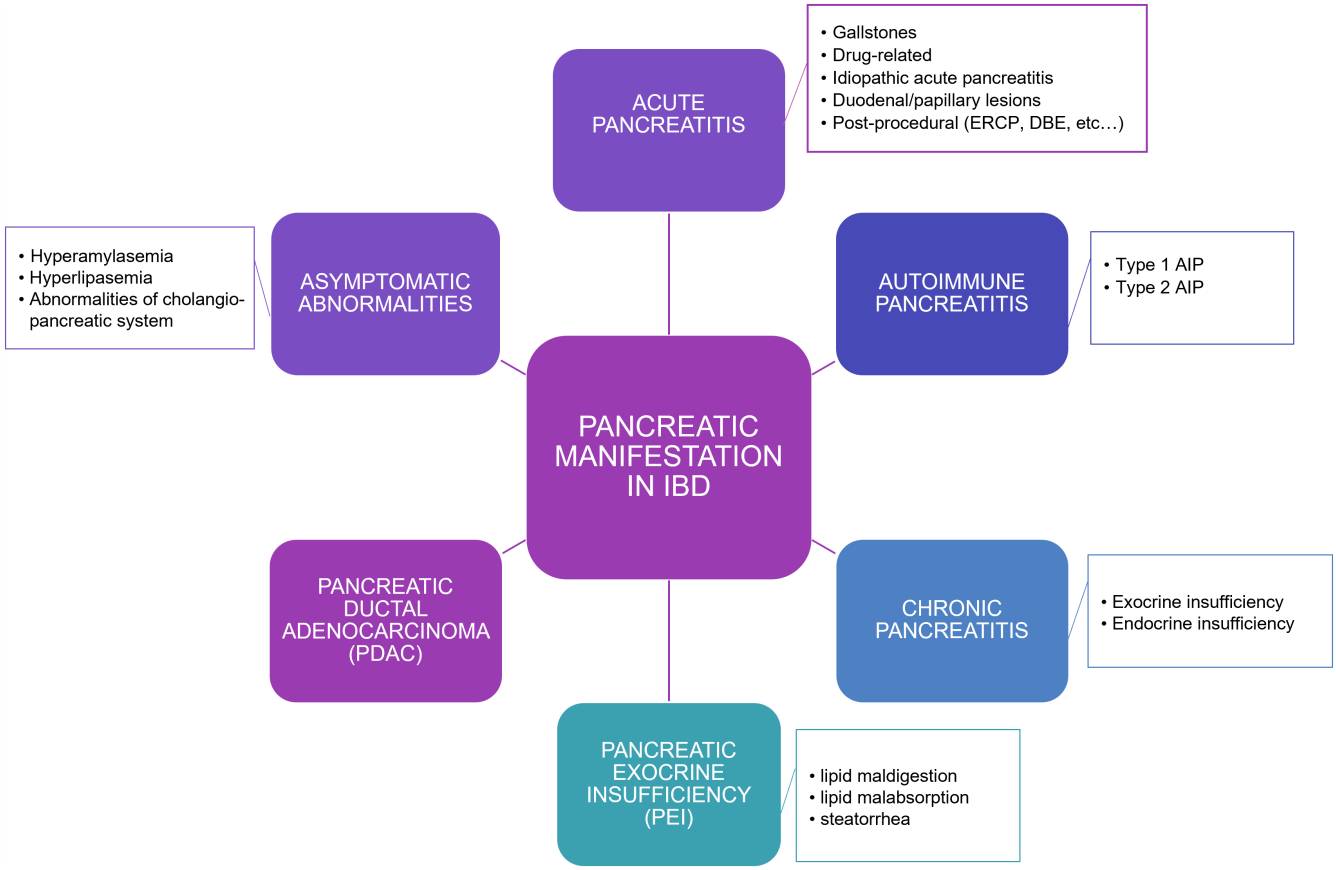

FIGURE 3 The spectrum of pancreatic manifestation in inflammatory bowel disease (IBD)

Diagnostic workup is generally similar to the general population, even if in patients with IBD, diagnosis and management may represent a challenge for the clinicians, because of the aforementioned possible bias of interpretation of the clinical test for pancreatic function.

4 | CONCLUSION

Our study systematically reviewed the association between IBD and pancreatic diseases, which resulted consistent for AP, mainly due to gallstones and drugs. Even if rare, AIP shows a strong association with IBD, especially between type 2 AIP and UC. Asymptomatic abnormalities may be as frequent as 11%–14%. The wide spectrum of pancreatic involvement in patients with IBD (Figure 3) may represent a challenge to the clinician facing patients with IBD. In fact in these patients, acute abdominal pain may occur due to the IBD itself or its acute intra-abdominal complications. The biochemical tests to examine the pancreatic function, including amylase and lipase in patients with IBD, can be affected by a high fraction of false positives that do not exactly reflect an actual AP.

On the other hand, the possibility of pancreatic involvement should not be overlooked and the clinicians facing patients with IBD should be aware of it. A collaborative approach with a pancreas specialist may be the most productive route to manage these patients.

AUTHORSHIP

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AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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