ORIGINAL ARTICLE

Inflammatory Bowel Diseases Elevate the Risk of Developing Acute Pancreatitis

A Meta-analysis

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Objectives: Increasing data suggest that acute pancreatitis (AP) occurs more frequently among patients with inflammatory bowel diseases (IBDs) than in the non-IBD population; however, currently no comprehensive meta-analysis is available.

Methods: Systematic literature search was conducted in 4 major databases. We included observational studies sampling from the general population. Basic study characteristics and crude incidences of AP were extracted. Pooled odds ratios (ORs) with 95% confidence interval (CIs) were calculated using the random-effects model. Subgroups were set up by Crohn disease and ulcerative colitis. Heterogeneity was tested with I^2 statistics.

Results: Eight studies were eligible for the analysis. The odds of AP were 3 times higher in IBD (OR, 3.11; 95% CI, 2.93–3.30; I^2, 0.0%), significantly higher in Crohn disease than in ulcerative colitis ($P < 0.001$; OR, 4.12 vs OR, 2.61; I^2, 0.0%). The pooled annual incidence of AP in IBD was 210/100,000 person-years (95% CI, 84–392/100,000 person-years; I^2, 98.66%).

Conclusions: We confirmed that IBD elevates the risk of AP and of 100,000 IBD patients 210 AP cases are to be expected annually. Therefore, it is important to include pancreatic enzyme level measurements and radiological investigations in the workup of IBD patients with acute abdominal pain.

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Received for publication April 30, 2020; accepted July 19, 2020.

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Gábor Veres, Deceased January 28, 2020.

Supported by Project Grants titled "GINOP-2.3.2-15-2016-00048 – STAY ALIVE" and "EFOP-3.6.2-16-2017-00006 – LIVE LONGER" both co-financed by the European Union (European Regional Development Fund) within the framework of Programme Széchenyi 2020, ÚNKP-19-3-I-SE-80, and UNKP-19-4-PTE-236 by the New National Excellence Program of the Hungarian Ministry of Human Capacities.

The authors declare no conflict of interest.

B.T., ZS., P.H. and G.V. designed the research and the study concept. BT. and B.S. made the acquisition of data. N.G. analyzed and interpreted the data. B.T., N.G., P.V., and G.V. wrote the article. Z.S., A.G., and P.H. supervised the study. Z.K., K.M., E.H., and P.J.H. made critical revision of the manuscript for important intellectual content. All authors gave their final approval of the version of the article to be published. The authors had no writing assistance.

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

DOI: 10.1097/MPA.0000000000001650

Key Words: inflammatory bowel disease, acute pancreatitis, meta-analysis, epidemiology, extraintestinal manifestation, pancreatic involvement

(*Pancreas* 2020;00: 00–00)

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal (GI) tract that comprises Crohn disease (CD) and ulcerative colitis (UC). The number of affected patients has been growing in recent decades both in adults and children creating an increasing burden on GI units.[1] Inflammatory bowel disease has a multifactorial etiology where genetic predisposition, environmental factors, and altered intestinal microflora could lead to the intestinal immune abnormalities that fuel the mucosal inflammation.[2] Although the main symptoms are connected to the GI tract, IBD is a systemic disease that often presents with associated conditions or extraintestinal manifestations (EIM): dermatologic, musculoskeletal, oral, ocular, cardiovascular, neurologic, hepatobiliary, or pancreatic lesions.[3,4]

The most common pancreatic pathologies associated with IBD are acute pancreatitis (AP) and asymptomatic pancreas enzyme level elevations (for a recent review, see Iida et al[5]). Acute pancreatitis is a sterile inflammatory condition of the pancreatic tissue characterized by the activation of pancreatic enzymes inside the pancreas for various reasons; the most common etiologies in the general population are biliary obstruction and excessive ethanol consumption.[6,7] Although these non–IBD-specific etiologies can be observed in IBD patients as well, several publications suggest that IBD is associated with an elevated risk for AP.[8–10] Based on case reports and cohort studies, 2 disease-specific forms of AP can be seen in IBD: one is most likely related to the pathogenesis of IBD and, therefore, can be considered as EIM of IBD, whereas the other form is a consequence of the management of IBD or its associated diseases (eg, biliary stones).[4] However, the distribution of these etiologies in IBD associated AP is yet to be explored. Likewise, to our knowledge, no comprehensive synthesis of the large-scale studies reporting the odds or the annual incidence of AP in IBD is available. Therefore, we aimed to explore, analyze, and systematically assess the current literature to provide evidence-based data on the association of AP and IBD.

MATERIALS AND METHODS

This study was reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[11] The review protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42017080464).

Search Strategy

A systematic search was conducted in 4 major electronic databases (MEDLINE via PubMed, Embase, Web of Science, Scopus) up to June 19, 2019 (date of the last search), without any search restrictions. The search strategy used comprehensive strings of words with variations of the terms "pancreatitis" in combination with term variations for "inflammatory bowel diseases," "Crohn's disease," or "ulcerative colitis." The exact search query used for the search can be found in Supplementary Table 1, http://links.lww.com/MPA/A823. The reference lists of selected articles were also checked.

Study Selection and Eligibility Criteria

Selection of the studies and screening was conducted by 2 investigators (B.T. and B.S.) independently. The screening was performed through a review of the titles and abstracts of the records. Studies that met the inclusion criteria and those with abstracts that lacked crucial information for the decision regarding their exclusion were retrieved for full-text evaluations. Decisions of eligibility and disagreements were resolved through discussion or by a third reviewer (G.V.). To be included in this review, studies had to meet all of the following criteria: (1) completed and published observational studies with human subjects, (2) the use of objective definitions of IBD and AP, (3) the provision of quantitative reports of IBD and AP, and (4) all participants had been counted only once in the published report. To appraise the odds of AP in IBD the following PECO was used: (P) general population, (E) IBD patients, (C) non-IBD population, and (O) odds of AP. Studies that did not report the incidence of AP either in the IBD or the non-IBD population or the reported data were redundant (ie, a participant could be counted more than once in the final report) were excluded. To examine the annual incidence of AP in IBD, we included studies sampling from the IBD population (P) and reporting incidence rates of AP (O) over an observation period given in person-years (PYs). Studies were not included if they reported only mean follow-up data or reported redundant data. Conference abstracts were excluded from both analyses. When studies reported the same population (database) and period, the most recent study was selected for inclusion.

Data Extraction

The same authors conducted the data extraction independently, and disagreements were resolved by consensus. Name of the first author, date of publication, geographical location, study type, study period, age-range of included individuals, the subtype(s) of IBD, number of IBD patients, crude incidence of AP cases (for IBD and non-IBD population, respectively), adjusted relative measures, and the observation period of the study in PYs were extracted using a data extraction table, if applicable (Table 1.).

Data Synthesis and Analysis

Odds ratios (ORs) were calculated from the crude incidences and pooled ORs or event rates with 95% confidence intervals (CIs) were calculated. We applied the random-effects model with the DerSimonian-Laird estimation.[18] Cochrane Q, I^2, and χ^2 tests were used to quantify statistical heterogeneity and gain probability values, respectively. Based on Cochrane handbook, $I^2 = 100\% \times (Q - df)/Q$ and represents the magnitude of the heterogeneity (I^2 = 30–60% – moderate; 50–90% – substantial; 75–100% – considerable heterogeneity), and $P < 0.1$ indicated significant heterogeneity.[19] All statistical analyses were performed using STATA 16.0 (Stata Corporation, College Station, Tex).

Risk of Bias and Quality of Evidence

Following the Cochrane Prognosis Methods Group recommendation,[20,21] the quality assessment of prognostic studies was made using the Quality in Prognosis Studies (QUIPS) tool. First, 6 important domains were critically appraised to evaluate validity and bias in the studies: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting.[20] Each domain contained between 3 and 7 prompting items to be rated on a 4- (yes/partial/no/unsure) or 2-grade scale (yes/no). In a final stage, the overall judgment of the risk of bias (RoB) within each domain was made based on the rated items; all of the responses to the prompting items were taken together when judging a domain's overall RoB, which was expressed on a 3-grade scale (high, moderate, or low RoB). Hence, the QUIPS assessment results in 6 ratings of RoB, 1 for each domain. The final RoB of each study was decided by the number of domains with high and low RoB: studies were considered to have low overall RoB if none of the 6 domains had high and most of the domains had low RoB; high overall RoB was judged when 2 or more domains had high RoB, or less than half of the domains had low RoB; otherwise, the overall RoB was judged to be moderate. To examine small study effects, we used the visual assessment of a funnel plot because tests for funnel plot asymmetry are not advised in analyses with fewer than 10 studies.[22]

Ethics Approval

Ethical approval was not required as data is not individualized, and primary data were not collected.

RESULTS

Search and Study Selection

The search of 4 electronic databases resulted in 9178 records (Embase 3540, Scopus 3132, Web of Science 1198, and PubMed 1308), of which 3627 nonduplicate articles were screened by title and abstract. One additional article was found eligible based on reference lists of the studies screened by full text.[16] The overview of screening and study selection is shown in Figure 1. The articles selected for full-text screening were handled together for the 2 analyses (143 articles were screened). From a total of 8 articles, 6[9,10,14–17] and 4[9,12–14] studies were included in the 2 final analysis, respectively. The basic characteristics and main findings of the 8 articles included in our study are shown in Tables 1 and 2.

Analysis of the Odds of AP in IBD

We first analyzed the odds of AP in IBD. Of the 6 eligible studies, 1 was cross-sectional, 2 were prospective cohort, and 3 case-control studies; the (*International Coding of Diseases* [*ICD*]-based) definition of cases was defined to be AP in all case-control studies,[10,15,16] and the control groups had been selected accordingly. The 6 articles contained data of 1,309,278 people from Denmark, Sweden, South Korea, and Taiwan. The pooled odds of AP in IBD was 3 times higher (OR, 3.11; 95% CI, 2.93–3.30; I^2 = 0.0%; Fig. 2) compared with the non-IBD population.

Of the 6 studies, 3 reported incidences of AP events broken down to CD and UC subpopulations and, therefore, were eligible for subgroup analysis. The analysis has found that the odds of AP in CD patients was significantly higher than that in UC patients (OR, 4.12; 95% CI, 3.75–4.54; I^2 = 0.0% vs OR, 2.61; 95% CI, 2.40–2.83; I^2 = 0.0%; $P < 0.0001$; Fig. 3).

TABLE 1. Basic Characteristics of the Eight Included Studies

Author, Year	Country	Study Period	Study Design	IBD Subgroup	Basis of Diagnosis	Age Range, y	Observation Period (PYs)	No. IBD Patients	No. Controls (Non-IBD)
Chen et al, 2016[9]	Taiwan	2000–2010	Prospective cohort	All IBD patients	*ICD-9* codes	≥20	63,532	11,909	47,636
Kim et al, 2017[12]	South Korea	1989–2015	Retrospective cohort	UC patients only	Medical records	9–90	33,355	33,386	N/A
McAuliffe et al, 2015[13]	United States	2004–2011	Retrospective cohort	All IBD patients	*ICD-9* codes	18–80	59,148	3307	N/A
Munk et al, 2004[10]	Denmark	1991–2002	Case-control	All IBD patients	*ICD-8* and *ICD-10* codes	N/A	N/A	94	17,409
Rasmussen et al, 1999[14]	Denmark	1977–1992	Prospective cohort	All IBD patients	*ICD-8* codes	N/A	112,824	15,526	15,526
Sundstrom et al, 2006[15]	Sweden	1995–1998	Case-control	All IBD patients	Medical records	20–85	N/A	28	2215
Thisted et al, 2006[16]	Denmark	1996–2003	Case-control	All IBD patients	*ICD-8* and *ICD-10* codes	N/A	N/A	129	28,264
Yang et al, 2018[17]	South Korea	2014	Cross-sectional	All IBD patients	*ICD-10* codes	19–75	N/A	43,281	1,127,261

N/A indicates no data published.

Analysis of the Annual Incidence of AP in IBD

Four studies reported the incidence rates of AP among IBD patients with the time of observation period given in PYs: 2 prospective and 2 retrospective studies. Three studies observed all IBD patients, including both CD and UC patients, whereas 1 study followed up only UC patients. The 4 studies covered a sum of 268,859 PYs observation time. The pooled incidence rate of AP in IBD was 0.21% (95% CI, 0.084%–0.392%), for example, 210/100,000 PYs (95% CI, 84–392/100,000 PYs). The forest plot of the analysis is shown in Figure 4.

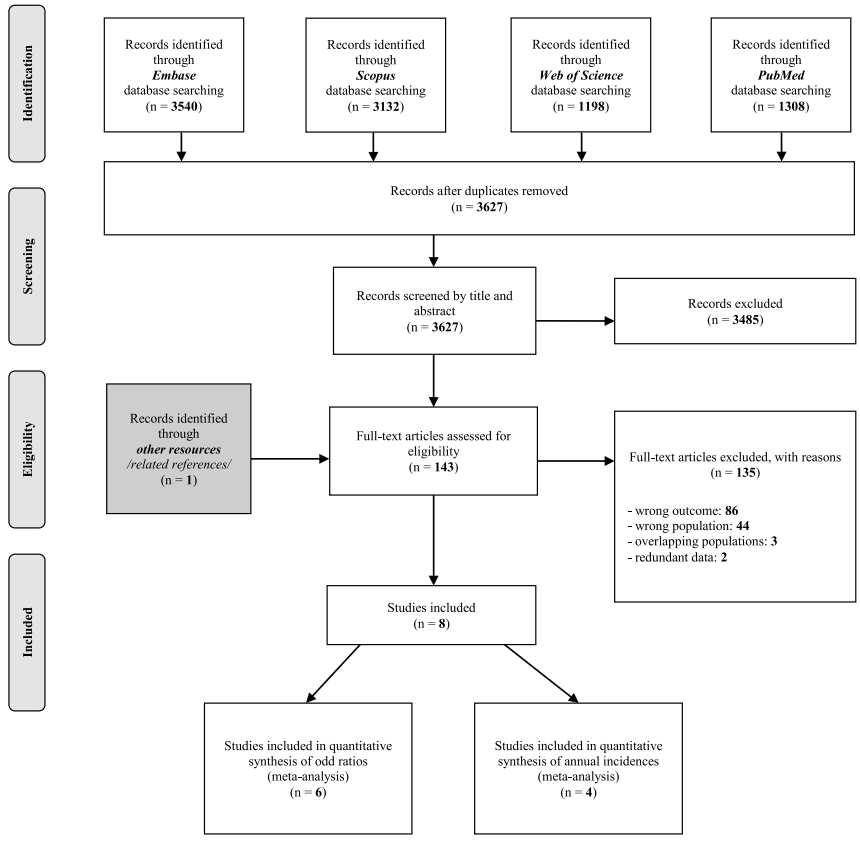

FIGURE 1. PRISMA flowchart.[11]

TABLE 2. Effect Estimates of the Eight Included Studies

Author, Year	OR* (Overall)	OR* (CD)	OR* (UC)	Annual Incidence Per 100,000 PYs	Adjusted Measures Reported	Measures Adjusted for
Chen et al, 2016[9]	3.24	N/A	N/A	318	Hazard ratio: CD: 3.4 (95% CI, 2.7–3.26) UC: 2.49 (95% CI, 1.91–3.26)	Age, sex, alcohol-related disease, biliary stone, hypertension, hyperlipidemia, diabetes mellitus, obesity, hepatitis B and C, COPD, hypertriglyceridemia, cardiovascular disease, chronic kidney disease, hypercalcemia
Kim et al, 2017[12]	N/A	N/A	N/A	153	N/A	N/A
McAuliffe et al, 2015[13]	N/A	N/A	N/A	360	N/A	N/A
Munk et al, 2004[10]	2.90	4.28	1.77	N/A	N/A	N/A
Rasmussen et al, 1999[14]	2.73	4.33	2.09	76	Standardized incidence ratio: CD: 4.3 (95% CI, 2.9–6.2) UC: 2.1 (1.6–2.8)	Sex, age
Sundstrom et al, 2006[15]	3.94	N/A	N/A	N/A	OR: IBD: 4.7 (95% CI, 2.2–10)	Sex, age
Thisted et al, 2006[16]	2.80	N/A	N/A	N/A	N/A	N/A
Yang et al, 2018[17]	3.11	4.12	2.64	N/A	Standardized prevalence ratio: CD: 4.94 (95% CI, 4.47–5.40) UC: 2.48 (2.28–2-68)	Sex, age

*Crude ORs, calculated based on published data.

COPD indicates chronic obstructive pulmonary disease; N/A, no data published.

Heterogeneity and Quality Assessment of Data

The assessment of the odds of AP in IBD proved to be homogeneous ($I^2 = 0.0\%$; $P = 0.848$), whereas high heterogeneity was detected ($I^2 = 98.66\%$; $P < 0.001$) in the analysis of the annual incidence of AP in IBD. In this latter case, because of the low number of studies, the source of heterogeneity could not be investigated by any further subgroup analysis.

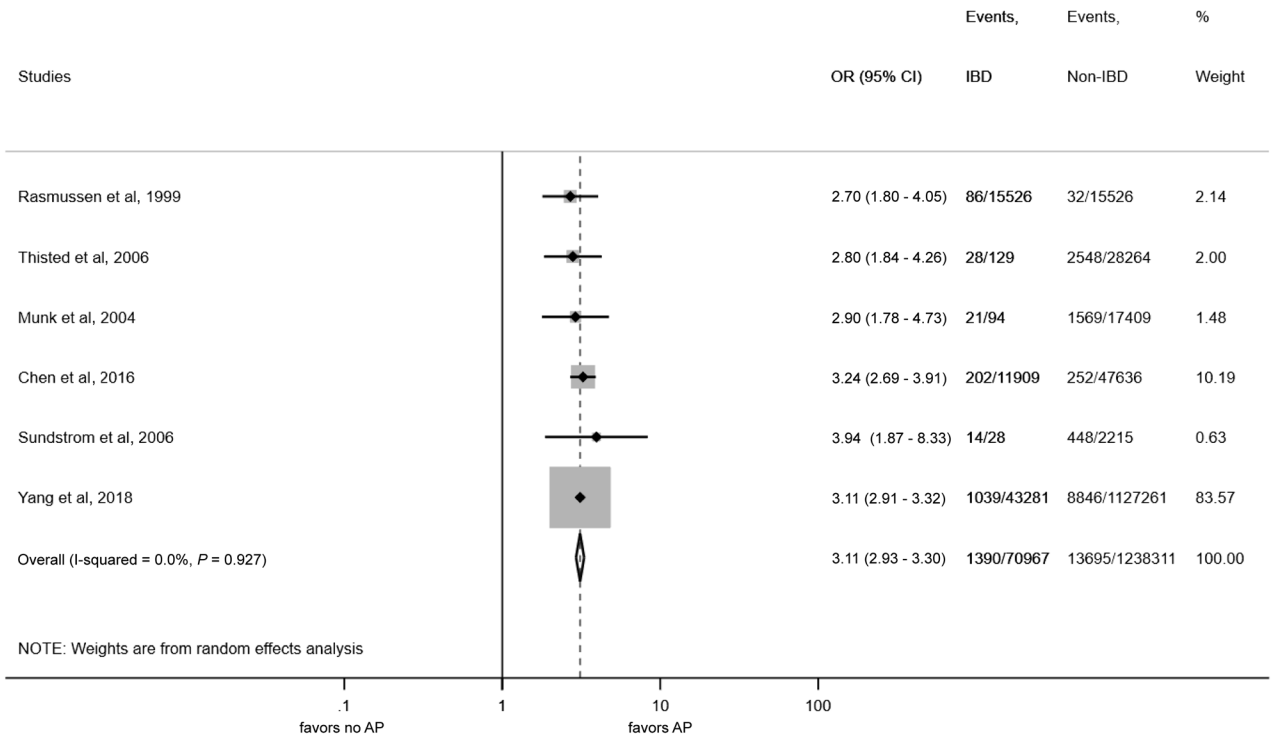

FIGURE 2. Pooled ORs of AP in IBD (vs non-IBD population).

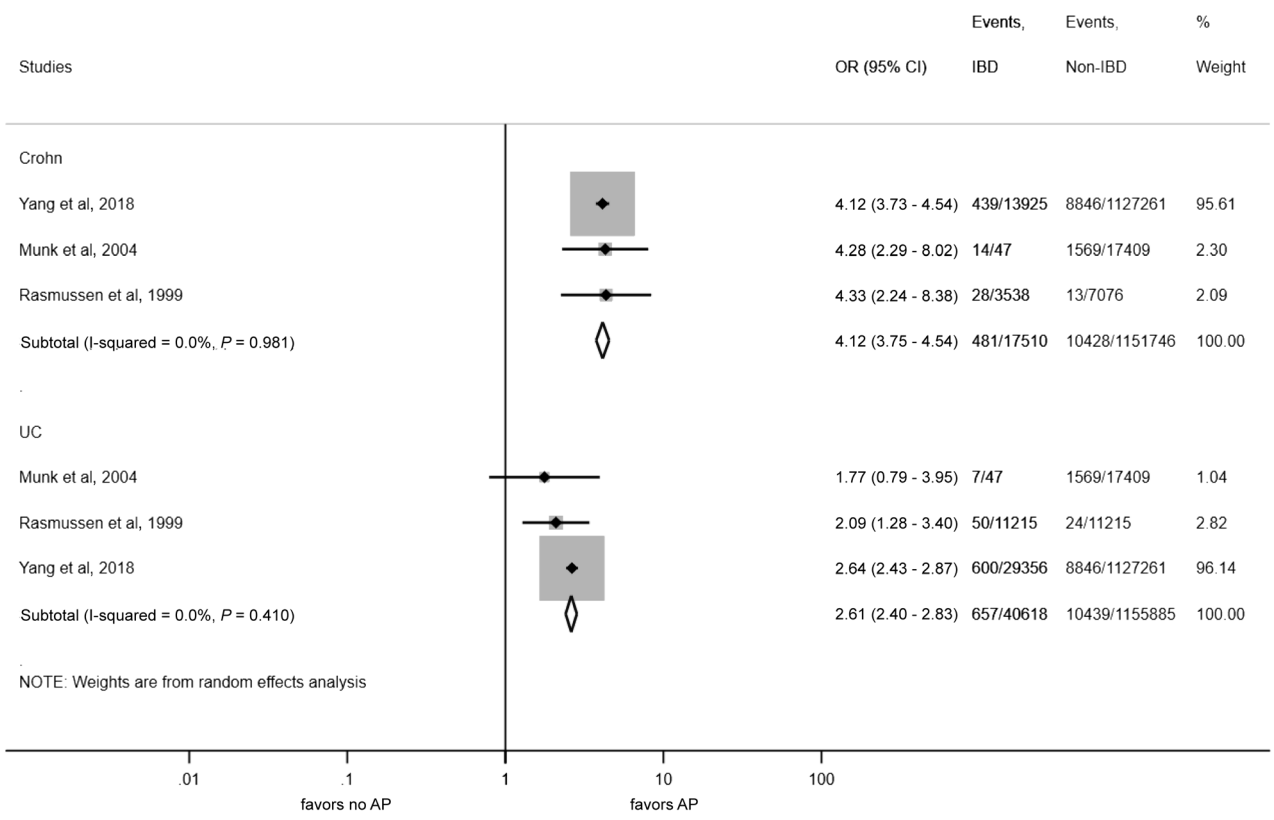

FIGURE 3. Pooled ORs of AP in CD and UC.

Risk of bias of the included articles in the 2 analyses was assessed by 6 domains, respectively using the QUIPS tool (Supplementary Table 2, http://links.lww.com/MPA/A823).

In the analysis of ORs, the overall quality of included studies was high: RoB was low in 5 and moderate in one of the 6 articles. Study participation, outcome (AP) measurement, and statistical

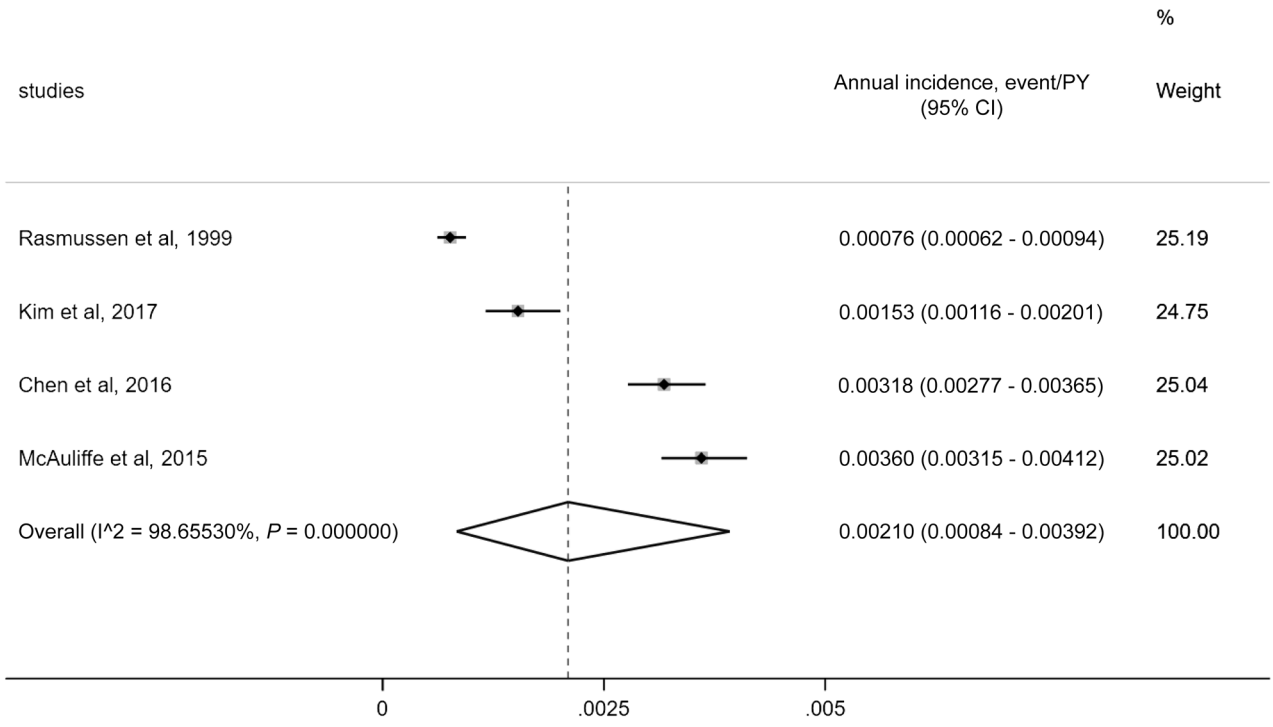

FIGURE 4. The pooled annual incidences of AP in IBD.

analysis and reporting domains were judged to have low RoB in all included studies. The study attrition domain was assessed only in prospectively recruiting studies[9,14,15] and was found to have moderate RoB in all 3 studies. There was 1 study with moderate RoB in the measurement of prognostic factor (IBD) domain and 2 in the Study confounding domains, respectively; all other studies had low RoB in these domains (Supplementary Table 2A, http://links.lww.com/MPA/A823). Visual assessment of the funnel plot suggested no serious small study effects.

In the analysis of the annual incidence, the overall quality of the included articles is moderate: RoB was low in one and moderate in 3 of the 4 studies. The measurement of prognostic factor (IBD) and statistical analysis domains received low RoB judgment for all studies. The study participation and the study confounding domains were judged to be low once and moderate thrice. The RoB of the study attrition domain was assessed only in the prospective studies and was found to be moderate in both cases. The outcome (AP) measurement domain was of moderate RoB in one study and low in the other 3 studies (Supplementary Table 2B, http://links.lww.com/MPA/A823). Because of the type of outcome measure (event rates), the presence of publication bias could not be ruled out.

DISCUSSION

Acute pancreatitis is a potentially serious inflammatory disorder with a possibly high mortality rate.[23,24] The leading symptom of AP is acute abdominal pain. Beside others, AP can occur in association with IBD, where the clinical symptoms of the 2 condition may be difficult to differentiate. In IBD, acute abdominal pain may occur because of a severe relapse of the disease, subileus (as a consequence of strictures), or an intra-abdominal abscess. The overlapping symptoms of AP and these complications may delay the appropriate diagnostic workup such as the measurement of serum lipase and amylase levels. Since the early management of AP is crucially important,[25,26] increased surveillance leading to an earlier diagnosis may save patients' lives.

In the last 50 years, an emerging number of case reports and clinical studies suggested that AP is more frequent in IBD; however, the number of population-wide studies and therefore, firm evidence addressing this association is limited. To our knowledge, this current meta-analysis is the first to investigate the association between AP and IBD. We aimed to summarize the currently available findings of large-scale studies. We have concluded that the pooled odds for AP in IBD is 3 times higher (OR, 3.11) than in the non-IBD population (Fig. 2), the odds are higher in CD than in UC (Fig. 3), and the pooled annual incidence is 210/100,000 PYs (Fig. 4). The number of studies and the reported data has proved to be insufficient for a more detailed stratification, including analysis of etiological distribution.

Ball et al[27] suggested at first an association between pancreatic involvement and IBD based on autopsy studies of UC patients. In the current guidelines and reviews, AP is the most frequently mentioned pancreatic lesion in IBD[4,28–30]; however, no clear recommendations for the optimal clinical diagnostic workup are stated. This may be explained by the variety of contributing etiologies and the lack of firm evidence. Because the current hypotheses on the possible background mechanisms causing this association between AP and IBD are strongly connected to the different etiologies of the pancreatic inflammation, and, therefore, are hard to discuss independently, we also wanted to synthesize the available evidence. However, we were unable to find suitable data for the quantitative synthesis of the different etiologies of AP in IBD. Therefore, we can only give a summary of the possible etiologies with some reference to the possible mechanisms of the connection between AP and IBD.

In IBD, the etiology of AP can be divided into 3 groups.[4] Some AP cases share common pathogenetic pathways with IBD and, therefore, could be considered as EIMs of IBD: these are the cases of autoimmune, granulomatous, idiopathic, and primary sclerotizing cholangitis associated pancreatitis (provided that they occur in association with IBD). Another major group of AP cases associated with IBD is related to the medical treatment of the disease: drug-induced (especially thiopurine-induced), post-endoscopic retrograde cholangiopancreatography (ERCP), postenteroscopy pancreatitis, and AP secondary to duodenal CD are in this group.[4] Besides the previously mentioned causes, the group of "classical" etiologies (eg, biliary obstruction, ethanol abuse) also occurs; however, there is major controversy on the proportion of these 3 groups of etiologies in the published studies.

One of the possible candidates that are presumed to be causing the elevated number of AP cases in IBD is biliary obstruction.[5] In the general population, cholelithiasis can be responsible for up to 40% of the cases[31] and several studies show an elevated risk for cholelithiasis in IBD.[32–34] However, studies focusing on AP in IBD were so far unable to undoubtedly confirm biliary pancreatitis as a major factor behind the elevated chance of AP in IBD. Moolsintong et al[35] retrospectively analyzed the clinical features and outcomes of 48 CD patients with AP in the United States between 1976 and 2001 and found that biliary and idiopathic AP were equally frequent, each corresponding for 21% of cases, followed by alcohol abuse (15%), duodenal CD (15%), thiopurine-induced AP (13%), and post-ERCP pancreatitis (10%). Later, in a large Spanish cohort, Bermejo et al[8] found that the most of AP cases were attributed to drug exposure (64%), whereas 20% were idiopathic, 12% biliary, and 4% of miscellaneous etiology (duodenal CD, post-ERCP, hypertriglyceridemia, etc). Another team analyzed all the hospital admissions during 2005 and 2011 with a primary diagnosis of AP and a co-diagnosis of IBD in the United States, but they focused only on alcohol and drug abuse, and biliary etiologies.[36] They have shown that alcohol abuse was also recorded in approximately 12% of cases (11.6% in CD and 12.1% in UC) and 21% of controls. The rate of cases attributable to medications was found to be significantly higher in CD (6.8% vs 4.9%) but not in UC, and they observed the diagnosis of biliary obstruction less frequently in IBD compared with controls (2.4% vs 4.4%), both in CD and UC. The latest study addressing the etiology of AP in UC from a single referral center in South Korea has shown that 45% of patients had drug induced (of which 55% thiopurine), 25% had autoimmune, 18% idiopathic, and 12% gall stone–induced pancreatitis, but they have not evaluated alcohol abuse.[12]

In summary, it seems that "classical" risk factors including biliary obstruction, similarly to the general population, have an important role in IBD, but the proportion of the reported etiologies in different studies vary highly. Another important candidate behind the elevated chance of AP in IBD is medical treatment-associated pancreatitis. Accordingly, most of the studies uniformly document a significant proportion (up to 65%) of drug-induced pancreatitis, especially thiopurine-induced cases.

Although thiopurine-induced pancreatitis (TIP) is usually considered as a mild complication of IBD because the clinical course of the most cases is mild,[37] patient with TIP might require the discontinuation of the ongoing thiopurine therapy and a choice of a more complex treatment.[38] Thiopurine-induced pancreatitis usually occurs within the first 30 days after the start of treatment, in 1.5% to 7% of treated patients.[8,12,37,39,40] Bermejo et al[8] reported that 56% of AP cases in their IBD cohort were related to thiopurine exposure and most cases was seen in CD (65% vs 22% of all AP cases in CD and UC, respectively). In a recent study, pediatric

IBD patients during azathioprine treatment had an almost 6 times higher chance for AP compared with no treatment with azathioprine (ratio of incidence rates, 5.82; 95% CI, 2.46–13.72); incidence rate of AP was 49.1 event per 1000 PYs during treatment.[39] Another interesting finding is that azathioprine-induced pancreatitis was found more frequently in CD (4.9%) compared with other conditions treated with azathioprine (autoimmune hepatitis (1.5%), renal transplantation (0.5%), and liver transplantation (0.4%) and 0% in UC, rheumatoid arthritis, systemic lupus berythematosus, or Wegener granulomatosis, $P < 0.05$).[41] Although the sex distribution of all AP cases in IBD was found shifted toward males in population-based studies,[9,14] a slight female dominance was observed in several reports of TIP in IBD.[42–46]

In our analysis, we originally aimed to determine the proportion of the certain etiologies of AP associated with IBD; however, we did not reach this goal because of the low number of eligible studies and lack of published data on etiologies in the eligible ones. Furthermore, although we were able to confirm the association between AP and IBD, the causative relationship of the 2 could not be stated. Until we gather firm evidence either on the distribution of etiologies or on the causative connection between IBD and AP, this remains only an interesting association clinicians should be aware of. Therefore, to provide firm evidence, further large-scale studies dedicated to exploring the etiological distribution and the clinical course of AP in IBD are highly needed.

There are several strengths and limitations of this study, and therefore, the results of this meta-analysis should be treated with caution. The main strength of our study is the robust size of the pooled population and the use of the PRISMA guidelines. Another strength is that in our analysis, no heterogeneity was observed when pooling the ORs of AP in IBD ($I^2 = 0\%$).

There are also limitations to our study. One is the low number of eligible articles included, which consequently led to a limited number of analyses. Another major limitation is that the ORs reported in this meta-analysis are calculated based on the reported number of events in the investigated publications, and therefore, are crude ORs. Adjusted ORs for major risk factors of AP could not be calculated because of the lack of information. Pooled analysis of adjusted outcome measures was also not available because they were only reported for IBD in general in 1 study and both for CD and UC in 3 studies, and all studies used different outcome measures.

Because IBD is a heterogeneous disease, treating it as one homogeneous patient group, as our main analysis did, could lead to oversimplified and indirect results. However, we were able to conduct a subgroup analysis of 4 studies based on the IBD subtypes and, therefore, provide a clinically more relevant outcome. Unfortunately, none of the eligible studies addressed the occurrence of AP based on anatomic location or clinical behavior of IBD, which would allow further subgroup analyses and help describe the topic more precisely. Similarly, no comparison analysis could be made based on the etiology or behavior of AP, which also simplifies an otherwise complex outcome. In the analysis of annual incidence significant heterogeneity was seen ($I^2 = 98.67\%$), however, in prognostic studies with large sample sizes, a high heterogeneity could be observed frequently.[21] Another reason for the high heterogeneity observed in this analysis might be the different geographical and temporal distribution of the studies: the studies originated from Taiwan,[9] South Korea,[12] the United States,[13] and Denmark[14]; the Danish study was conducted in the 1990s, whereas the 3 others in the late 2010s.

In conclusion, in this first meta-analysis on the topic, we showed that the odds of AP in IBD is 3 times higher than that in the non-IBD population. Current clinical guidelines only mention AP as a possible EIM of IBD[4] but lack the recommendations for an optimal diagnostic workup to rule out AP in patients with abdominal complaints. Based on this meta-analysis, approximately 21 AP case per 10,000 IBD patient can be anticipated annually, which emphasize the importance of pancreatic enzyme measurements and pancreatic imaging examinations in symptomatic IBD patients. Because CD patients have significantly higher odds of AP than patients with UC, more thorough surveillance of pancreatic involvement in CD is advisable. Unfortunately, the etiology and clinical course of AP in IBD remain a topic, where further large-scale studies are needed.

ACKNOWLEDGMENTS

The authors offer this study to the memory of Prof. Gábor Veres.

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