Risk of pancreatitis in patients with inflammatory bowel disease – a meta-analysis

Josefine E. Pedersen[1], Lars H. Ängquist[1, 2], Camilla B. Jensen[1], Johan S. Kjærgaard[1], Tine Jess[1, 3] & Kristine H. Allin[1, 2]

ABSTRACT

INTRODUCTION: Patients with inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are believed to be at increased risk of pancreatitis. The objective of the present study was to investigate the association between IBD and risk of pancreatitis in a systematic review and meta-analysis.

METHODS: We conducted a systematic literature search in the PubMed and Embase databases. Data were extracted using predefined data fields, and risk of bias was assessed using the Risk of Bias Assessment tool for Non-randomized Studies. Random-effects meta-analyses were conducted.

RESULTS: Four studies with acute pancreatitis as outcome met the eligibility criteria. The overall estimated risk ratio revealed an increased risk for acute pancreatitis in patients with IBD of 2.78 (95% confidence interval (CI): 2.40-3.22). The risk ratio was increased for both CD and UC, with estimated risk ratios of 3.62 (95% CI: 2.99-4.38) and 2.24 (95% CI: 1.85-2.71), respectively. No studies meeting the eligibility criteria had chronic pancreatitis as outcome.

CONCLUSIONS: The risk of acute pancreatitis is increased in patients with IBD and higher for patients with CD. Due to the observational design of the studies included in our meta-analysis, the mechanisms underlying the increased risk of pancreatitis are unknown and remain to be investigated. Studies of the risk of chronic pancreatitis among patients with IBD are warranted.

FUNDING: This work was supported by a grant from the Novo Nordisk Foundation (NNF16OC0022586). The funder had no role in the study design, collection, analysis, interpretation of the data, or the writing of the manuscript.

TRIAL REGISTRATION: not relevant.

Inflammatory bowel disease (IBD) is an immune-mediated disease characterised by chronic intestinal inflammation with alternating periods of remission and relapse [1-4]. IBD, comprising ulcerative colitis (UC) and Crohn's disease (CD), is observed predominantly in developed countries; but after many years on the rise, the incidence now seems to have stabilised in the Western countries. Conversely, the incidence is now increasing in newly industrialised countries. Hence, the global burden of IBD is increasing substantially [5, 6].

Pancreatitis is characterised by inflammation in the pancreas and is categorised as either acute or chronic. Both acute and chronic pancreatitis are severe conditions that lead to hospitalisation and possibly death. The overall mortality rate in acute pancreatitis falls in the 2-9% range [7].An association between IBD and pancreatic lesions was initially reported by Ball et al in 1950: in an autopsy study, pancreatic inflammation was observed in 53% of patients with UC compared with 3% in the control group [8]. Subsequently, other studies have reported an association between IBD and pancreatitis [9]; however, a recent case series did not find an increased incidence of pancreatitis in patients with IBD compared with the general population [10].

Several mechanisms have been suggested to underlie a potential association between IBD and pancreatitis [11]. One hypothesis is that pancreatitis is an extra-intestinal manifestation of IBD [12] and thus related to a shared pathogenic pathway. Another hypothesis is that pancreatitis is caused by the management of IBD, especially by medications, or by associated diseases, especially gall stones [9]. The aim of the present study was to investigate the association between IBD and risk of pancreatitis by conducting a systematic literature review and meta-analysis of observational studies reporting on the risk of pancreatitis in patients with IBD as compared with IBD-free individuals.

METHODS

A systematic review of the existing literature addressing the association between IBD and the risk of pancreatitis was performed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [13] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [14].

KEY POINTS

- Based on four high-quality studies, we showed that patients with inflammatory bowel disease (IBD) are at increased risk of developing acute pancreatitis compared with non-IBD individuals.
- The risk is most pronounced in patients with Crohn's disease who are at a three-fold increased risk of developing acute pancreatitis, whereas patients with ulcerative colitis have a two-fold increased risk.
- We identified no eligible studies with chronic pancreatitis as outcome.
- Future research should investigate the underlying mechanisms, which may involve medications, surgery or a shared pathogenic pathway.

META-ANALYSIS

1) Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark
2) Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen
3) Department of Epidemiology Research, Statens Serum Institut, Denmark

Dan Med J 2020;67(3):A08190427

Eligibility criteria

Eligible studies included observational studies investigating a study population of adult patients with IBD and comparing this population with a non-IBD population. Studies were included if the outcome was acute pancreatitis and/or chronic pancreatitis. Studies of children, animal studies, case reports and reviews were excluded.

Information sources and search strategy

To identify relevant studies addressing the risk of pancreatitis among patients with IBD, a literature search with no language restrictions was performed in PubMed and Embase from database inception until October 2018. A variation of synonyms of the exposure "inflammatory bowel disease", the outcome "pancreatitis" and the study design "epidemiologic studies" was combined into search strings. The complete search strategy including specific search strings is presented in the **supplementary figure**. Additionally, we systematically reviewed the reference lists of the eligible studies.

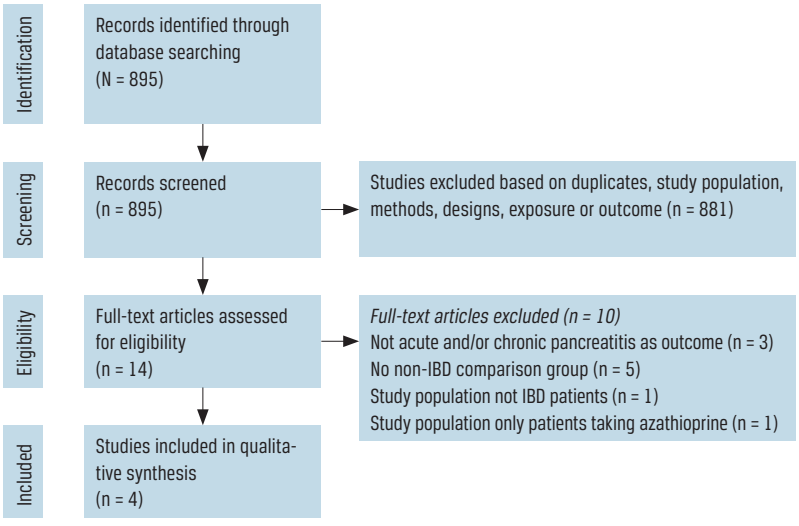
Study selection

Two authors independently screened titles and abstracts. After this initial screening, 14 articles were read in full to identify studies meeting the eligibility criteria.

Data collecting process and data forms

Data extraction was conducted for the studies eligible for inclusion in the systematic review. The data items included were: author, year of publication, country, study design, source population and period of time, sample size, statistical analysis including covariates, and main findings. When both crude and adjusted estimates were presented in the included articles, the adjusted estimates were extracted for the systematic review and meta-analysis.

FIGURE 1 / Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow chart illustrating the literature search.



Risk of bias

Risk of bias was assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [15]. Based on RoBANS, the studies were categorised as having an overall low risk of bias (≤ 1 domain evaluated as having a high or unclear risk of bias), medium risk of bias (two domains evaluated as having a high or unclear risk of bias) or high risk of bias (≥ 3 domains evaluated as having a high or unclear risk of bias). To evaluate how well the studies accounted for potential confounders, a list of major confounding variables was defined. As major risk factors for developing pancreatitis include alcohol use, gall stone disease, and medication, and as these variables may also be associated with IBD, they had to be adjusted for through study design or statistical modelling, for a study to be assessed as "low risk" in the domain "Confounding variables".

Data synthesis and analysis

The studies included in the meta-analysis reported different types of effect estimates – odds ratios, standardised incidence ratios or hazard ratios – but as these estimates are all closely related to measurements of relative risk and hence support the same interpretation, we found it acceptable to here compare and combine the estimates through meta-analysis. For one study [16], which only reported separate estimates for CD and UC, we derived the estimate for IBD simply by adding the observed and expected number of cases for each subtype, and subsequently calculating the 95% confidence interval (CI) assuming a Poisson distribution of observed cases. Statistical heterogeneity was tested using the chi-squared test and measured by the I^2 statistic. The effect estimates were combined based on a random effects meta-analysis approach where studies are weighted based on corresponding standard errors [17]. Since the heterogeneity parameter was here consistently estimated to be zero, in practice fixed effects meta-analyses were performed ($I^2 = 0.0\%$; for all p-values: $p \geq 0.41$). Analyses were derived both for IBD and specifically for CD and UC. Furthermore, estimates were combined on the log-risk ratio scale and then finally back-transformed to the original scale. All statistical analyses were carried out in Stata 14.2 (StataCorp LLC, College Station).

RESULTS

Data retrieval

A total of 895 articles were identified through literature

TABLE 1 / Overview of studies evaluating risk of acute pancreatitis among patients with inflammatory bowel disease.

Reference	Country	Study design	Source population and period	Sample size	Statistical analysis	Main findings (95% CI)
Rasmussen et al, 1999 [16]	Denmark	Prospective cohort study Mean follow-up 7 yrs	Nationwide, 1977-1992	15,526 IBD patients	SIR calculated by sex, 5-yr age groups and 5-yr calendar periods[a]	SIR = 4.3 (2.9-6.2) for CD SIR = 2.1 (1.6-2.8) for UC
Blomgren et al, 2002 [18]	Sweden	Case-control study	Multi-region: 4 regions in Sweden, 1995-1998	462 cases of AP 1,781 controls	Logistic regression models Adjusted for sex, age, BMI, alcohol use, tobacco use, co-morbidities and selected medications	OR = 3.4 (1.5-7.9) for IBD
Munk et al, 2004 [19]	Denmark	Case-control study	Single region: North Jutland County, 1991-2002	1,590 cases of AP 15,913 controls	Logistic regression models Adjusted for use of azathioprine, glucocorticoids, sulfasalazine and a history of gall stone and alcohol-related disease	OR = 3.7 (1.9-7.6) for CD OR = 1.5 (0.7-3.6) for UC
Chen et al, 2016 [20]	Taiwan	Prospective cohort study Mean follow-up 6 yrs	Nationwide, 2000-2010	11,909 IBD patients 47,636 age-matched patients without IBD	Cox proportional hazard models Adjusted for age, sex and co-morbidities	HR = 2.93 (2.40-3.58) for IBD HR = 3.40 (2.70-4.28) for CD HR = 2.49 (1.91-3.26) for UC

AP = acute pancreatitis; CD = Crohn's disease; CI = confidence interval; HR = hazard ratio; IBD = inflammatory bowel disease; OR = odds ratio; SIR = standardised incidence ratio; UC = ulcerative colitis.

a) Observed number of AP in the IBD cohort was divided by the expected number based on national incidence rates calculated by sex, 5-yr age groups and 5-yr calendar periods.

TABLE 2 / Quality assessment: Risk of Bias Assessment tool for Non-randomized Studies.

Reference	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting	Overall risk of bias[a]
Rasmussen et al, 1999 [16]	Low	High	Low	Low	Low	Low	Low
Blomgren et al, 2002 [18]	Low	Low	Low	Low	Low	Low	Low
Munk et al, 2004 [19]	Low	High	Low	Low	Low	Low	Low
Chen et al, 2016 [20]	Low	High	Low	Low	Low	Low	Low

a) Low risk of bias: ≤ 1 domain evaluated as "high domain risk of bias"; medium risk of bias: 2 domains evaluated as "high domain risk of bias"; high risk of bias: ≥ 3 domains evaluated as "high domain risk of bias".

search and their titles and abstracts were screened for eligibility (**Figure 1**). Among those, 881 were excluded as the title and abstract revealed that the studies were not eligible. After full-text reading, an additional ten articles were excluded (Figure 1) and, finally, four studies [16, 18-20] were included in our systematic review and meta-analysis.

Study characteristics

Characteristics of the four included studies are presented in **Table 1**. All four studies had acute pancreatitis as outcome. The studies were published between 1999 and 2016. Two studies were from Denmark, one from Sweden and the latest study was from Taiwan. Two of the studies were register-based prospective cohort studies. The two other studies were case-control studies, one based on register data and one based on structured interviews. We found no eligible studies with chronic pancreatitis as outcome.

Risk of bias within and across studies

To assess the risk of bias of the included studies, the RoBANS tool was used (**Table 2**).

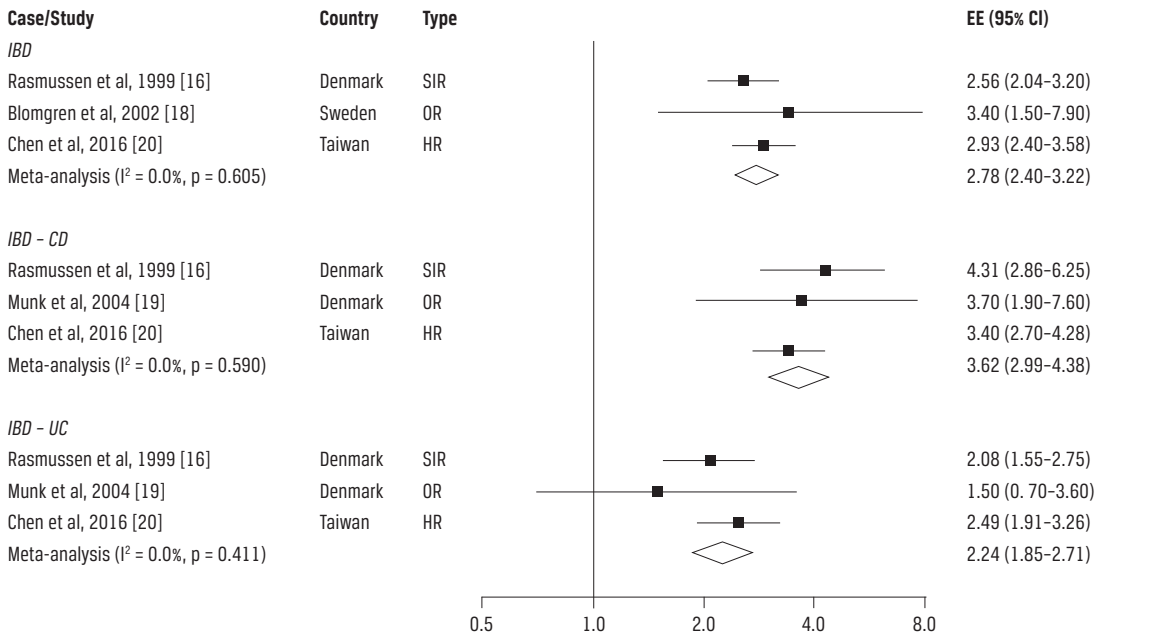
All studies were of a high quality and were evaluated as having a low overall risk of bias. The only domain in which all the studies except one were evaluated as having a high risk of bias was the domain regarding confounding variables. The studies included were all relatively new (published in the 1999-2016 period).

The study populations were all based on large study cohorts of patients with a distinct IBD diagnosis and non-IBD subjects (numbers ranging from 2,243 to 59,545), based on register data or from structured interviews. The age and sex distribution of the study population was comparable across the four studies.

All studies were from developed countries with three studies based on Scandinavian study populations and one study based on an Asian study population.

FIGURE 2 /

Forest plot of the estimated risk ratios of acute pancreatitis among patients with inflammatory bowel disease.
Squares indicate risk ratios, and whiskers indicate 95% CI. Diamonds indicate overall meta-analysed risk ratios (for all p-values: p ≤ 0.001).



CD = Crohn's disease; CI = confidence interval; EE = effect estimate; HR = hazard ratio; IBD = inflammatory bowel disease; OR = odds ratio; SIR = standardised incidence ratio; UC = ulcerative colitis.

Funnel plots did not indicate asymmetry, but plots based on few studies should be interpreted with caution.

Risk of acute pancreatitis in patients with inflammatory bowel disease

Two studies provided risk estimates of acute pancreatitis for IBD patients overall [18, 20]. Additionally, for one study [16], which only reported separate estimates for CD and UC, we were able to derive the estimate for IBD overall as explained in the Methods section. Risk estimates of acute pancreatitis for IBD patients overall ranged from 2.56 (95% CI: 2.04-3.20) to 3.40 (95% CI: 1.50-7.90). Three studies provided risk estimates of acute pancreatitis for CD and UC [16, 19, 20], with risk estimates ranging from 3.40 (95% CI: 2.70-4.28) to 4.31 (95% CI: 2.86-6.25) for CD and from 1.50 (95% CI: 0.70-3.60) to 2.49 (95% CI: 1.91-3.26) for UC (Table 1).

The studies included in this systematic review all found an increased risk of acute pancreatitis in patients with IBD. Accordingly, the overall estimated risk ratio revealed a significantly increased risk of acute pancreatitis in patients with IBD of 2.78 (95% CI: 2.40-3.22; $p < 0.001$) (**Figure 2**). The risk of acute pancreatitis was significantly increased for both CD and UC, with the highest risk observed in patients with CD: the overall estimated risk ratio was 3.62 (95% CI: 2.99-4.38; $p < 0.001$) for patients with CD and 2.24 (95% CI: 1.85-2.71; $p < 0.001$) for patients with UC.

DISCUSSION

The present systematic review and meta-analysis shows that patients with IBD are at increased risk of developing acute pancreatitis compared with non-IBD individuals. The risk is most pronounced in patients with CD, who are at a three-fold increased risk of developing acute pancreatitis, whereas patients with UC have a two-fold increased risk. We identified no eligible studies with chronic pancreatitis as outcome.

To our knowledge, this is the first systematic review and meta-analysis investigating the risk of pancreatitis in patients with IBD compared with non-IBD individuals. Previous reviews have included case series or focused on the spectrum of pancreatic disorders in patients with IBD [9, 11]. Another strength of the present study is our thorough literature search with two authors screening all titles and abstracts. Furthermore, the included studies were systematically evaluated to ensure that only studies of a high quality were included in the meta-analysis. Using the RoBANS tool for bias assessment, we found all included studies to have an overall low risk of bias. However, three of the four studies were evaluated as having a high risk of bias in the specific domain of confounding variables, wherefore lack of control for confounding represents a potential limitation to this systematic review. Moreover, only four studies met the inclusion criteria, limiting evaluation of publication bias and subgroup effects.

The mechanisms underlying the increased risk of acute pancreatitis, especially in patients with CD, are

not well described. Pancreatitis may represent an extra-intestinal manifestation of IBD [12] related to a shared pathogenic pathway. This type of pancreatitis comprises idiopathic pancreatitis but also autoimmune pancreatitis, which has been associated with IBD in recent years [21, 22]. Medical treatment of IBD, especially azathioprine [23], or co-morbidities per se, particularly gallstones, have been shown to lead to an increased risk of pancreatitis [9]. However, two of the studies [16, 20] included in our meta-analysis did not take information on medication use into account, and two studies [18, 19] included only information on selected medication use.

Therefore, the medications used for treatment of IBD likely contribute to the increased risk of pancreatitis observed in our meta-analysis. In support of this notion, a recently published Swedish-Danish nationwide cohort study of children with IBD showed a considerably increased risk of acute pancreatitis among children initiating azathiopurine therapy [24]. The increased risk of pancreatitis found in patients with IBD could also be explained by surveillance bias, as patients are followed closely and examined thoroughly in the course leading to IBD diagnosis and during the period after IBD diagnosis. A diagnosis of acute pancreatitis is generally based on two of the following three criteria [25]: 1) acute and sudden abdominal pain; 2) increase in serum amylase and/or lipase greater than > 3 times upper limit; 3) characteristic findings on contrast enhanced-computed tomography/ultrasound/magnetic resonance.

However, if surveillance bias was to explain the observed association between IBD and pancreatitis, one would expect the risk to be similar among patients with CD and UC, as there are no major differences in examination and follow-up programmes for the two subtypes of IBD. Moreover, as one would expect patients with clinical symptoms of pancreatitis to seek medical help due to pain, regardless of an IBD diagnosis, surveillance bias seems less likely.

CONCLUSIONS

With this systematic review and meta-analysis of observational studies of acute pancreatitis among patients with IBD as compared with non-IBD individuals, we conclude that patients with IBD are at increased risk of developing acute pancreatitis. The risk of acute pancreatitis is three-fold increased in CD and two-fold increased in UC, whereas the risk of chronic pancreatitis in patients with IBD remains unknown. The studies included in the present meta-analysis only provide limited information on factors possibly contributing to the observed increased risk of pancreatitis in IBD. Hence, it is of clinical relevance to further study the impact of disease severity, co-morbidities, surgery and IBD medications including biologic drugs on risk of acute pancreatitis among patients with IBD. Moreover, studies of the risk of chronic pancreatitis among patients with IBD are warranted.

CORRESPONDENCE: *Kristine H. Allin.*
E-mail: kristine.allin@regionh.dk
ACCEPTED: 24 January 2020
CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

LITERATURE

1. Gomollon F, Dignass A, Annese V et al. 3rd European Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management. J Crohn Colitis 2017;11:3-25.
2. Gionchetti P, Dignass A, Danese S et al. 3rd European Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: surgical management and special situations. J Crohn Colitis 2017;11:135-49.
3. Harbord M, Eliakim R, Bettenworth D et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohn Colitis 2017;11:769-84.
4. Magro F, Gionchetti P, Eliakim R et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohn Colitis 2017;11:649-70.
5. Molodecky NA, Soon IS, Rabi DM et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46-54.
6. Ng SC, Shi HY, Hamidi N et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769-78.
7. Lankisch PG, Blum T, Maisonneuve P et al. Severe acute pancreatitis: when to be concerned? Pancreatology 2003;3:102-10.
8. Ball WP, Baggenstoss AH, Bargen JA. Pancreatic lesions associated with chronic ulcerative colitis. Arch Pathol (Chic) 1950;50:347-58.
9. Ramos LR, Sachar DB, DiMaio CJ et al. Inflammatory bowel disease and pancreatitis: a review. J Crohn Colitis 2016;10:95-104.
10. Pezzilli R, Pagano N. Benign exocrine pancreatic diseases in inflammatory bowel diseases. Dig Dis 2017;35:449-53.
11. Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. J Clin Gastroenterol 2010;44:246-53.
12. Harbord M, Annese V, Vavricka SR et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohn Colitis 2016;10:239-54.
13. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
14. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
15. Kim SY, Park JE, Lee YJ et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 2013;66:408-14.
16. Rasmussen HH, Fonager K, Sorensen HT et al. Risk of acute pancreatitis in patients with chronic inflammatory bowel disease. A Danish 16-year nationwide follow-up study. Scand J Gastroenterol 1999;34:199-201.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
18. Blomgren KB, Sundstrom A, Steineck G et al. A Swedish case-control network for studies of drug-induced morbidity - acute pancreatitis. Eur J Clin Pharmacol 2002;58:275-83.
19. Munk EM, Pedersen L, Floyd A et al. Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. Am J Gastroenterol 2004;99:884-8.
20. Chen YT, Su JS, Tseng CW et al. Inflammatory bowel disease on the risk of acute pancreatitis: a population-based cohort study. J Gastroenterol Hepatol 2016;31:782-7.
21. Roque Ramos L, DiMaio CJ, Sachar DB et al. Autoimmune pancreatitis and inflammatory bowel disease: case series and review of the literature. Digest Liver Dis 2016;48:893-8.
22. Tsen A, Alishahi Y, Rosenkranz L. Autoimmune pancreatitis and inflammatory bowel disease: an updated review. J Clin Gastroenterol 2017;51:208-14.
23. Teich N, Mohl W, Bokemeyer B et al. Azathioprine-induced acute pancreatitis in patients with inflammatory bowel diseases - a prospective study on incidence and severity. J Crohn Colitis 2016;10:61-8.
24. Wintzell V, Svanstrom H, Olen O et al. Association between use of aza-

thioprine and risk of acute pancreatitis in children with inflammatory bowel disease: a Swedish-Danish nationwide cohort study. Lancet Child Adolesc Health 2019;3:158-65.
25. Banks PA, Bollen TL, Dervenis C et al. Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.