Inflammatory bowel disease does not alter the clinical features and the management of acute pancreatitis: A prospective, multicentre, exact-matched cohort analysis

Short title: Inflammatory bowel disease and acute pancreatitis

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List of abbreviations

AP	acute pancreatitis
BISAP	bedside index of severity in acute pancreatitis
CRP	C-reactive protein
CD	Crohn's disease
IAP	International Association of Pancreatology
APA	American Pancreatic Association
IBD	inflammatory bowel disease
IS	immunosuppressed
IQR	interquartile range
LOH	length of hospitalization
NIS	non-immunosuppressed
RR	relative risk
SD	standard deviation
UC	ulcerative colitis
WBC	white blood cells

Abstract

Objective and aims: Acute pancreatitis in inflammatory bowel disease occurs mainly as an extraintestinal manifestation or a side effect of medications. We aimed to investigate the prognostic factors and severity indicators of acute pancreatitis and the treatment of patients with both diseases.

Design: We performed a matched case-control registry analysis of a multicentre, prospective, international acute pancreatitis registry. Patients with both diseases were matched to patients with acute pancreatitis only in a 1:3 ratio by age and gender. Subgroup analyses were also carried out based on disease type, activity, and treatment of inflammatory bowel disease.

Results: No difference in prognostic factors (laboratory parameters, bedside index of severity in acute pancreatitis, imaging results) and outcomes of acute pancreatitis (length of hospitalization, severity, and local or systemic complications*)* were detected between groups. Significantly lower analgesic use was observed in the inflammatory bowel disease population. Antibiotic use during acute pancreatitis was significantly more common in the immunosuppressed group than in the non-immunosuppressed group ($p=0.017$). However, none of the prognostic parameters or the severity indicators showed a significant difference between any subgroup of patients with inflammatory bowel disease.

Conclusion: No significant differences in the prognosis and severity of acute pancreatitis could be detected between patients with both diseases and with pancreatitis only. The need for different acute pancreatitis management is not justified in the coexistence of inflammatory bowel disease, and antibiotic overuse should be avoided.

Keywords: acute pancreatitis, inflammatory bowel disease, antibiotics, disease management

What is already known on this topic

- the courses and therapy of acute pancreatitis in patients with inflammatory bowel disease do not differ from the general population
- the acute inflammation of the pancreas may complicate the course of inflammatory bowel disease
- prompt identification of the aetiology and management of pancreatitis is essential to avoid further complications in both pancreatitis and inflammatory bowel disease

What this study adds

- the prognostic parameters of acute pancreatitis did not differ between patients with or without inflammatory bowel disease
- severity parameters of acute pancreatitis did not show significant differences between patients with or without inflammatory bowel disease
- the need for analgesia was significantly lower in patients with both diseases, and the antibiotic use was significantly higher in the immunosuppressed subgroups of patients with inflammatory bowel disease

How this study might affect research, practice or policy

- overuse of antibiotics in the treatment of acute pancreatitis should be avoided as there is no benefit
- antibiotics are not required in immunosuppressed patients with inflammatory bowel disease
- our findings should be analysed in more extensive prospective cohort studies of patients with IBD, with different therapeutic regimens and disease activity.

Introduction

Inflammatory bowel diseases (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic gastrointestinal conditions characterized by relapsing and remitting patterns. Various extraintestinal manifestations with 6 to 47% frequency may also occur, such as arthropathies, erythema nodosum, episcleritis, primary sclerosing cholangitis, and, less frequently, lung, heart, or pancreatic involvement.[1] Due to the increasing incidence of IBD,[2] disease-related complications, e.g., pancreatic manifestations, will also occur more frequently.[3] Possible pathological changes in the pancreas can range from innocent elevation of pancreatic enzymes to more severe disorders,[4] such as acute, chronic, autoimmune pancreatitis, and exocrine dysfunction.[5,6] In a recent meta-analysis by Pedersen *et al.*, patients with CD had a higher incidence of acute pancreatitis (AP) than those with UC, but both were higher than the general population (relative risk [RR]=3.62, 95%CI: 2.99-4.38, p=0.001; RR=2.24, 95%CI: 1.85-2.71, p=0.001, respectively).[7]

The first association between IBD and AP was reported by Ball *et al.*, in 1950, in an autopsy study.[8] Further studies have since reported strong associations between IBD and AP.[9] To date, several possible correlations between IBD and AP have been investigated,[3] including AP as an extraintestinal manifestation and the effect of various IBD drugs,[10] as well as well-known general etiological factors of AP.[9] According to the literature, the most common causes of AP in patients with IBD are choledocholithiasis and drugs.[9,11,12] Drugs are classified into definite, probable, and questionable categories based on their ability to induce AP.[13] Among the medications used in patients with IBD, 5-aminosalicylic acids[14,15] and azathioprine were associated definitely,[12,16-19] while metronidazole and corticosteroids were found probably to be associated with drug-induced AP.[6,20] Although corticosteroids are listed as possible causes of AP; a recent meta-analysis has shown the potential benefits of steroids in the coexistence of severe AP and IBD flares.[21] In addition, combination therapy with tumor necrosis factor-α inhibitors appears to be associated with a reduced risk of AP in patients taking mesalamine, thiopurines, or both.[22] In contrast to the potential benefits of tumor necrosis factor-α inhibitors, another biological agent, vedolizumab, may be associated with an increased risk of AP in adults and children.[23,24]

To the best of our knowledge, the courses and therapy of AP in patients with IBD do not differ from the general population.[3,6] However, the acute inflammation of the pancreas may complicate the course of IBD, so prompt identification of the aetiology and management of pancreatitis is essential to avoid further complications in both pancreatitis and IBD.[6,25] Proper management of AP and IBD is necessary to minimize the length of

hospitalization (LOH), thereby also reducing the economic burden.[26-28] In case of suspicion of drug-induced AP, withdrawal of the drug is mandatory.[6]

Because of the increased incidence and heterogeneous etiological factors of AP in patients with IBD, several studies[12,24,25,29-31] and reviews evaluated their association from different perspectives.[3,9,20,32,33] However, a pancreatic registry has never been used to analyse the characteristics of AP in patients with IBD and to correlate the clinical parameters of AP between patients with or without IBD. In the present study, we collected information from the Hungarian Acute Pancreatitis Registry on patients with both AP and IBD and analysed their data compared to the AP population without IBD and in subgroups of IBD. We aimed to investigate differences in prognostic factors, severity indicators, and drug use between patients with AP or those with co-existing AP and IBD.

Methods

The Hungarian Acute Pancreatitis Registry received ethical approval from the Scientific and Research Ethics Committee of the Medical Research Council (22254e1/2012/EKU) in 2012, and all patients analysed provided written informed consent. In the registry, a four-tier quality control system was applied to ensure data quality, described in detail in a previous publication from the registry.[34,35] The study protocol conforms to the ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in a prior approval by the institution's human research committee. This cohort study follows the STROBE statement for observational cohort studies.[36]

Design, setting, and participants

Adult patients (over 18 years of age) with AP were consecutively involved in this international, multicentre Hungarian Acute Pancreatitis Registry operated by the Hungarian Pancreatic Study Group (HPSG) between 2012 and 2020. Registry-based, exact-matched cohort analyses were performed from a database of 2,459 patients at a 1:3 match ratio. The IBD subjects were patients with both AP and IBD, and the non-IBD ones were patients with AP without IBD. Non-IBD subjects were selected based on exact gender and age data compared to IBD participants. The nationality of patients in both groups was Hungarian.

Data sources and outcomes

Diagnoses of AP and IBD were made according to current guidelines of the International Association of Pancreatology/American Pancreatic Association (IAP/APA), which states that AP requires two of the following three criteria: lipase or amylase levels three times the upper limit of normal, physical symptoms consistent with pancreatitis, and imaging findings. The European Crohn's and Colitis Organisation, and the European Society of Gastrointestinal and Abdominal Radiology. [37,38]

Patients were followed daily during their hospitalization for AP, and their detailed data were collected into an electronic database (e.g., baseline demographics, disease characteristics, and outcome variables). Additional information on IBD was collected from the hospitals' electronic medical records. Disease activity was determined by the Crohn's disease activity index (CDAI) for CD and the Mayo score for UC at the time of admission with AP.[39,40] Based on the pharmacological treatment of IBD used during the AP episode, patients were

classified as immunosuppressed (IS; intravenous or oral steroids, immunomodulatory, and biological therapy) and non-immunosuppressed (NIS; rectal steroid, budesonide, 5-aminosalicylic acids) patients.

From the electronic database, 29 variables of each AP case and additional 9 variables representing IBD were collected in our cohort. (Supplementary Table 1. A, B) The severity of AP, local complications, and organ failure were categorized according to the modified Atlanta criteria.[41]

Our outcomes included the examination of prognostic parameters of AP in the IBD and non-IBD patient groups (laboratory parameters [on admission C-reactive protein /CRP/, white blood cells /WBC/, creatinine, procalcitonin] and imaging results [abnormal pancreatic structure, ascites], bedside index of severity in acute pancreatitis /BISAP/, smoking and drinking habits),[42] severity indicators (severity, mortality, LOH, local and systemic complications, peak level of CRP and WBC, intensive care treatment), and applied therapy during hospital stay (need for antibiotics, analgesics).

Study size and statistical analyses

A total of 2,459 AP cases were collected prospectively with daily follow-up in the registry. 2,170 discharge files were uploaded and read by DD and PS to avoid information bias, check comorbidities, and search for missing information about IBD. Patients were followed up until the end of their hospitalization. Patients were excluded from the corresponding analyses in the case of missing data.

Before the detailed analyses, representativeness analyses were performed to investigate selection bias. Descriptive statistics on cohort characteristics were also carried out. Central tendencies (median and mean) and measures of dispersion (interquartile range [IQR] standard deviation [SD], range) were calculated for continuous variables, whereas incidence was determined for categorical ones. Below, the median with IQR is used because of the non-normal distribution of the data. The control subjects were precisely matched by gender and age in a 1:3 ratio. Firstly, all statistical analyses comparing IBD and non-IBD populations were performed with the controls randomly selected in a 1:1 ratio to obtain detailed results with *p* values. In case of missing data, the participant was excluded from that specific analysis.

Secondly, subgroups of IBD were compared as well, based on disease type (CD vs. UC), immunosuppression therapy (IS vs. NIS), and disease activity (clinical relapse vs. clinical remission).

Depending on the data distribution, Wilcoxon-Mann-Whitney was used for the continuous variables and Fisher's exact test or the chi-square test for the categorical ones. A *p*-value less than 0.05 (< 0.05) was defined as statistical significance. All calculations were performed with R statistical language (R version 4.1.0, R Core Team, Vienna, Austria, 2021).[43]

Results

Study population

Of the 2,459 enrolled patients with AP, 289 were excluded due to missing final reports. Further investigations were performed on 2,170 patients. The representativeness analysis demonstrated that our cohort presents the same epidemiological (age, gender, body mass index, aetiology) and major outcome distribution (severity, mortality, LOH) as the total cohort. Thus, our cohort population describes a general AP population. (Supplementary Figure 1)

A detailed review of 2,170 final medical AP records confirmed 27 cases of IBD as an IBD population. (Figure 1) The non-IBD population without the diagnosis of IBD was precisely matched by age and sex from the Hungarian Acute Pancreatitis Registry (n=81). All patients were followed until discharge. The patients involved may have had other comorbidities; they were not involved in the description and analysis due to their significant variances. The baseline characteristics of the IBD and non-IBD groups are summarized in Table 1. A. Twenty-nine AP episodes were diagnosed in 27 patients with IBD, including 14 patients with CD and 13 with UC. Twelve of the 27 patients were in relapse, while 15 patients were in remission during the AP episode. Nine patients were identified with IS and 17 with NIS treatment. Between the patients with IBD and without IBD, body mass index was significantly lower in the IBD population (p=0.001). (Supplementary Figure 2) The baseline clinical features of IBD at the time of AP are summarized in Table 1. B.

Table 1.A Baseline characteristics of the inflammatory bowel disease (IBD) and non-IBD groups

Characteristics		*IBD patients (n = 27)*	*non-IBD patients (n = 81)*	p-values
Age, median (IQR)		42 (32-62.5)	42 (32-62.5)	/
Gender, male, n (%)		15 (55.6)	45 (55.6)	/
Drinking habits: drinker, n (%)		9 (33.3)	39 (48.2)	p_1=0.57; p_2=0.17; p_3=0.57
Smoking habits: smoker, n (%)		9 (33.3)	24 (29.6)	p_1=1.00; p_2=1.00; p_3=0.35
Aetiology of acute pancreatitis, n (%)	*Alcohol*	1 (3.7)	14 (17.3)	/
	Biliary	5 (18.5)	36 (44.4)	
	Drug induced	8 (29.6)	0 (0.0)	
	Combined	0 (0.0)	9 (11.1)	
	Hypertriglyceridemia	0 (0.0)	3 (3.7)	
	Idiopathic	7 (25.9)	16 (19.8)	
	Other	6 (22.2)	3 (3.7)	
Severity of acute pancreatitis, n (%)	*Mild*	24 (88.9)	60 (74.0)	p_1=0.69; p_2=0.06; p_3=0.48
	Moderate	3 (11.1)	20 (24.7)	
	Severe	0 (0.0)	1 (1.2)	
Laboratory parameters, median (IQR)	*Amylase*	579 (317.5-1028.5)	701 (268-1536)	p_1=0.53; p_2=0.68; p_3=0.1
	Lipase	1349 (914-1995)	1439 (600.3-3419.8)	p_1=0.89; p_2=0.81; p_3=0.6
	Platelets	243.50 (180-311.5)	268 (225.5-338.3)	p_1=0.33; p_2=0.40; p_3=0.6

IBD: inflammatory bowel disease

Table 1.B Baseline characteristics of IBD patients

Characteristics			*IBD patients (n = 27)*
Type of IBD, n (%)	*CD*		14 (51.9)
	UC		13 (48.1)
Disease localization (Montreal classification), n (%)	*CD*	*ileum*	7 (53.8)
		ileocolonic	4 (30.8)
		colon	2 (15.4)
	UC	*left sided colitis*	4 (36.4)
		proctitis	4 (36.4)
		pancolitis	3 (27.2)
IBD treatment, n (%)	*Azathioprine*		5 (19.2)
	Biological therapy		1 (3.9)
	5-ASA		20 (76.9)
	Steroid		6 (23.0)
Immunosuppressed patients, n (%)			9 (34.6)
	Azathioprine		3 (33.3)
	Steroid		4 (44.4)
	Azathioprine + steroid		1 (11.1)
	Azathioprine + biological therapy		1 (11.1)
Activity of IBD, n (%)	*Patient in remission*		15 (55.6)
	Patient in relapse		12 (44.4)
Previous intestinal surgery, n (%)			4 (15.4)
Comorbidities, n (%)			17 (62.9)
Concomitant treatments, n (%)			18 (66.7)

IBD: inflammatory bowel disease; CD: Crohn's disease, UC: ulcerative colitis

Main results of prognostic parameters

Eight parameters (on-admission CRP, WBC, and serum creatinine, BISAP, smoking and drinking habits, imaging results of the pancreas, presence of ascites) were examined to investigate any difference between AP patients with or without IBD and between subgroups of the IBD population. Due to the high proportion of missing data, procalcitonin levels could not be examined. Of the 27 patients with IBD, procalcitonin was measured in only nine patients on admission, with a mean of 0.107 ng/ml (min-max: 0.02-0.29).

None of the laboratory parameters of prognostic factors showed significant differences between IBD and non-IBD cases (CRP: p=0.297; WBC: p=0.538; serum creatinine: p=0.794*).* (Figure 2. A-C) No differences were observed between the two groups in BISAP scores, pancreatic structure, or the presence of ascites (BISAP: p=0.832; pancreas structure: p=1.000; ascites p=0.203). (Figure 2. D-F) Almost the same proportion of patients from the two groups had BISAP 0 and 1 at diagnosis (56.2% vs. 52.4% and 37.5% vs. 28.6%, respectively), but fewer patients from the IBD group had BISAP 2 (6.2% vs. 14.3%). BISAP 3 occurred only in the IBD group (4.8%), and no BISAP 4 and 5 were observed. The rate of current alcohol consumption and smoking showed no differences either (33.3% vs. 48.1%; p=0.263, and 33.3% vs. 29.6%; p=0.810, respectively). (Supplementary Table 2)

On admission, WBC levels in NIS patients were significantly lower than IS patients. (p=0.007) (Supplementary Figure 3) Further prognostic parameters analysed did not show significant differences between subgroups of patients with IBD. See other results detailed in Supplementary Table 2.

Main results of the severity indicators

Six parameters (LOH, peak level of CRP and WBC, severity, local and systemic complications) were analysed to reveal differences between groups. None of the patients with IBD and AP died during follow-up, and none of the IBD patients were treated in the intensive care unit for AP; thus, mortality and intensive care treatment were not included in the analyses.

LOH (p=0.677*)* and peak levels of CRP (p=0.239) and WBC (p=0.432*)* did not show significant differences between the IBD and non-IBD populations. (Figure 3. A-C) There was no significant change in the severity of AP (p=0.384). However, the rate of moderate and severe cases was higher in the non-IBD group (mild: 89% vs. 74%, moderate: 11% vs. 24.7%, and severe: 0% vs. 1.2%). (Figure 3.D) None of the local or systemic

complications of AP showed a significant alteration between the groups examined (p=0.790 and p=0.328, respectively). (Figure 3. E-F, Supplementary table 2)

The three different IBD subgroup analyses demonstrated no significant alteration in the severity indicators. (Supplementary Table 3)

Inpatient treatment

Of the 27 cases in the IBD group, eight drug-induced AP were registered. The putative aetiological factors, azathioprine in three, and 5-aminosalicylic acids in five AP episodes, were stopped immediately.

Antibiotic treatment and pain management were studied to establish differences between groups and subgroups. Antibiotic treatment showed no significant differences (46.2% vs. 40.0%; p=0.642), but significantly more patients from the non-IBD group required analgesics than patients in the IBD group (55.6% vs. 80.6%; p=0.020). (Figure 4. A-B)

Antibiotic use was significantly higher in the IS group compared to the NIS group (p=0.017), although a clear indication (e.g., fistula or abscess) was not present. At the same time, there was no significant difference in antibiotic use between CD vs. UC and between patients with active or inactive disease. (Figure 5, Supplementary Table 3) No significant differences were found in antibiotics or analgesics use between patients with CD or UC and patients with active or inactive disease. (Supplementary Table 3)

Discussion

IBD is a chronic gastrointestinal condition characterized by intermitting relapsing and remitting patterns and the potential for extraintestinal manifestations. Due to the increasing incidence of IBD,[2] several cases of AP have been reported in association with IBD worldwide.[3,7] Since the association was first described in 1950, a number of strong correlations have been revealed. The most common aetiological factors for AP in patients with IBD are choledocholithiasis and IBD medications.[9,11,12] Appropriate treatment of AP, especially drug-induced pancreatitis in patients with IBD is crucial to avoid further complications and relapse after drug-withdrawal.

In this present study, we evaluated a cohort of patients with IBD in the Hungarian Acute Pancreatitis Registry and assessed in detail the differences of AP in patients with and without IBD. Due to the heterogeneity of aetiology, these factors were not evaluated and compared between groups. Although type 2 autoimmune pancreatitis can occur in association with IBD, this aetiology was not observed in our small cohort.

Firstly, several prognostic factors examined in our cohort did not reveal significant differences between AP patients with or without IBD. Our results are in line with the results of Jasdanwala *et al*., where the severity and prognosis of AP in patients with CD did not differ from the general population.[20] While, in other studies, the incidence of AP was higher in patients with CD,[12,26,44] nearly the same number of patients with CD or UC with the same characteristics of AP were registered in our cohort. Similar to the literature data, no differences in smoking and drinking habits were observed between our cohort's IBD and non-IBD populations.[13] The relationship between AP and disease activity remains questionable, as this previously released issue could not be confirmed in our cohort.[12] Although WBC levels were significantly higher in the IS subgroup than the NIS group, this difference was likely due to the low number of patients involved (alpha type error).

Secondly, various factors characterizing the severity of AP were examined, where no significant differences were found between groups and subgroups. In accordance with the literature data, the majority of AP cases from the IBD population were mild, with a small percentage being moderately severe.[12,20,30] No systemic complication was observed in our cohort, as in cases of mild to moderate AP, sterile inflammation remains in the pancreas.[25] No mortality was observed in IBD patients. As Alexoff *et al.* had previously reported, we found no longer hospital stays in patients with IBD and AP.[26]

Thirdly, the need for analgesia was significantly lower in the IBD population; we hypothesize that chronic illnesses may result in a higher pain tolerance threshold. Antibiotic use was significantly higher in the IS group than in the NIS group of patients with IBD. WBC counts on admission were significantly higher in the IS group,

but any parameter indicating a more severe form of pancreatitis or signs of IBD relapse cannot explain this clinical decision. We hypothesize that increased caution in patients taking IS may contribute to this significantly higher antibiotic use. In a review, Fousekis *et al*. stated that treatment of AP should not be different in patients with different comorbidities.[6] In laboratory or clinically unjustified cases, unreasonable drug therapy should be considered to reduce hospital costs, as the treatment of both AP and IBD is associated with high health care costs.[26] Moreover, unwarranted antibiotic therapy in IBD can lead to dysbiosis, which can cause acute flare-ups or affect the subsequent disease course of IBD.

According to the previous reviews, treatment of AP should not be modified in patients with IBD unless a disease flare-up coincides.[6,9] Treatment of moderate to severe AP in the setting of a flare of IBD may be challenging due to the conflicting literature on the effects of steroids on AP. According to Ramos et al., steroids may increase the risk of pancreatic necrosis and fluid collection.[9] In contrast, a recent meta-analysis revealed that steroid therapy does not worsen but improvs the outcome of severe AP.[45] In the case of flare-up of IBD, in addition to the known treatment of AP, the use of biologics instead of steroids, especially infliximab, has been considered.[6]

Although, ongoing concomitant treatment of IBD should not be stopped to avoid intestinal complications or flare-ups, but in cases where the IBD drug used is the putative aetiology of AP, immediate discontinuation is recommended because the generally mild, drug-induced AP responds rapidly to drug withdrawal.[12,29] Due to the high risk of recurrence of proven azathioprine or mercaptopurine induced AP, rechallenge of these drugs is contraindicated even at low doses.[46,47] A possible secondary expert opinion of the previously suspected triggering etiological factor may be necessary in the case of a chronic condition requiring drug treatment before the withdrawal of effective therapy.

Our present study has several strengths. This prospective cohort study collected daily clinical data with standardized question forms, thus minimizing information bias. Due to the study design, the changes between diagnosis and discharge provided better evidence of the results. We analysed the cohort's main epidemiological and outcome parameters compared to the whole cohort to minimize selection bias. Exactly matched control selection was used to compensate for the possible biases resulting from the small number of IBD cases.

Our cohort analysis has several limitations that suggest a careful interpretation of the results. As with most other cohort analyses, our clinical research question was defined post hoc, so not all aspects of AP-IBD could be investigated. The validity of our evaluation and results may be impaired by the small sample size of IBD patients. In addition to the small sample size, a lack of data allowed no further analyses. Patients excluded due to

missing final reports may contribute to selection bias. Furthermore, the analyses of the IBD subgroups were not feasible in the case-control design due to the low number of cases. There was a considerable variation in the aetiology of AP, so subgroup analyses based on this and further analyses of how aetiology may impact the course of AP were not feasible in the present study.

Conclusion

In summary, our results did not confirm any differences in the prognosis and severity of AP between patients with IBD and the general AP population, regardless of disease type and activity.[3] Overuse of antibiotics was observed in patients on immunosuppressive therapy, probably due to elevated levels of on admission WBC, platelet, and peak WBC counts. Based on our previous cohort analysis,[48] in agreement with the F17–18 recommendations in the IAP/APA guidelines,[37] overuse of antibiotics in the treatment of AP should be avoided as there is no benefit. Due to the same severity and prognostic results observed in the IBD population, antibiotics are not required in IS patients. Our findings should be analysed in more extensive prospective cohort studies of patients with IBD, with different therapeutic regimens and disease activity.

Authors' contribution

Conceptualization: DD, PS, methodology: NF, AV, PS, review of final reports: DD, PS; statistical analyses: NF, AV; writing-original draft preparation: DD, SP; visualization: DD, AV; review: BE, AP, ASz, PH and funding acquisition: AP, PH, PS

Data availability statement

The data underlying this article are available in the article and its online supplementary material.

Conflict of Interest

The authors have no conflicts of interest to declare.

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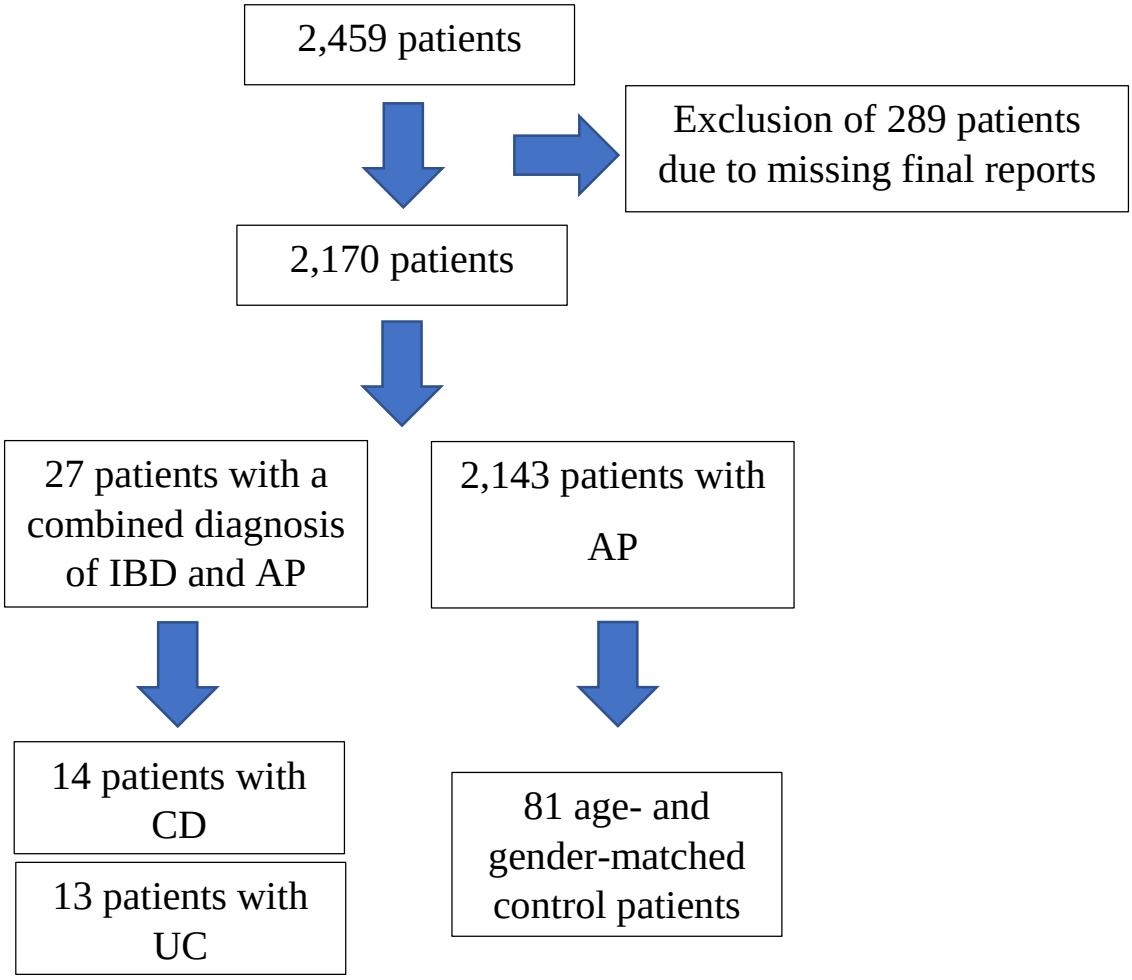


Figure 1. Flowchart of patient selection

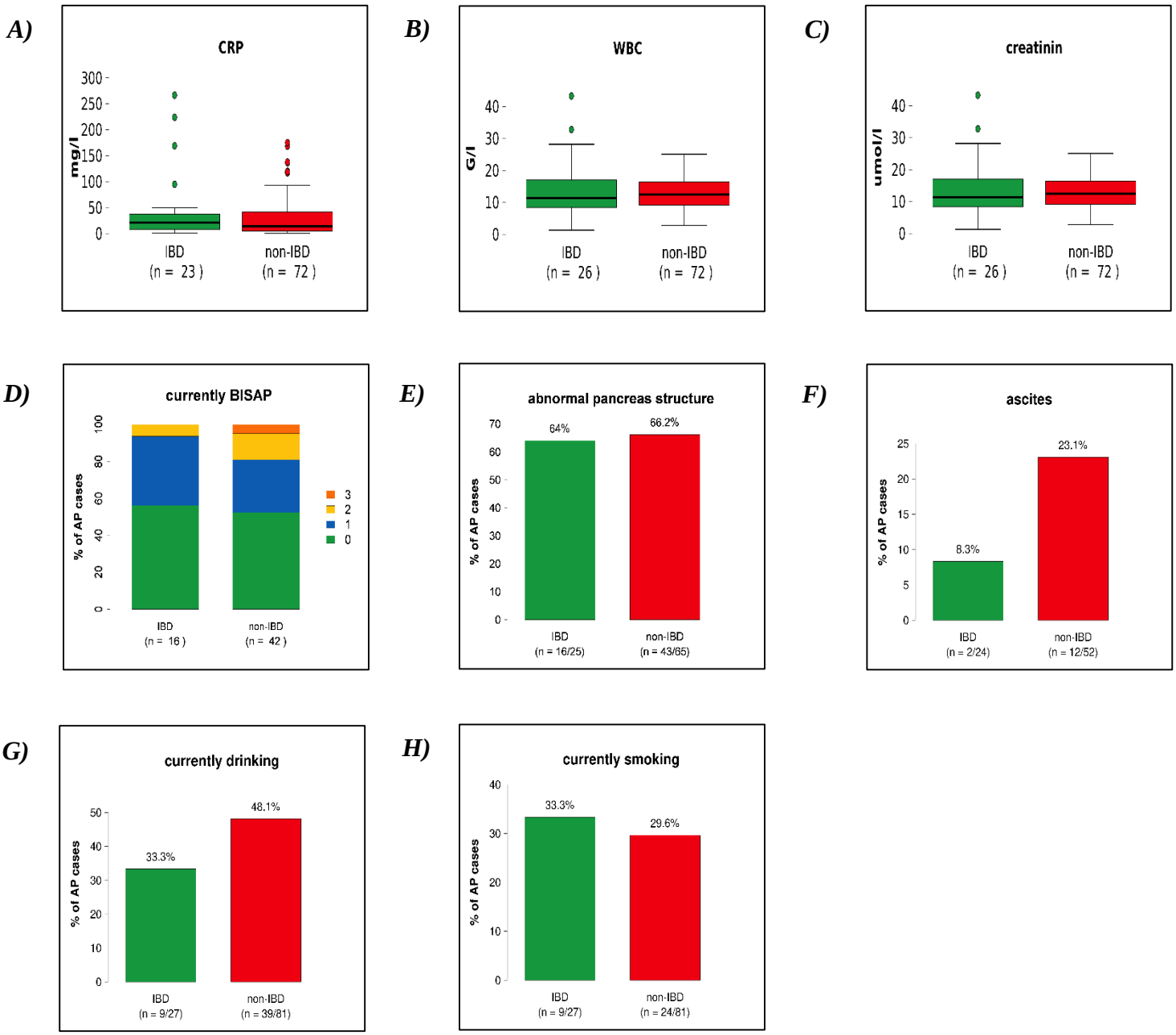


Figure 2 **Main results of prognostic parameters between inflammatory bowel disease (IBD) vs. non-IBD groups**

A) C-reactive protein (CRP; p=0.297); ***B)*** white blood cells (WBC; p=0.538); ***C)*** serum creatinine (p=0.794); ***D)*** bedside index of severity in acute pancreatitis (BISAP; p=0.832); ***E)*** pancreas structure (p=1.000); ***F)*** ascites (p=0.203); ***G)*** alcohol consumption (p=0.263); ***H)*** smoking (p=0.810)

N numbers (n) indicate the total number of cases in each group

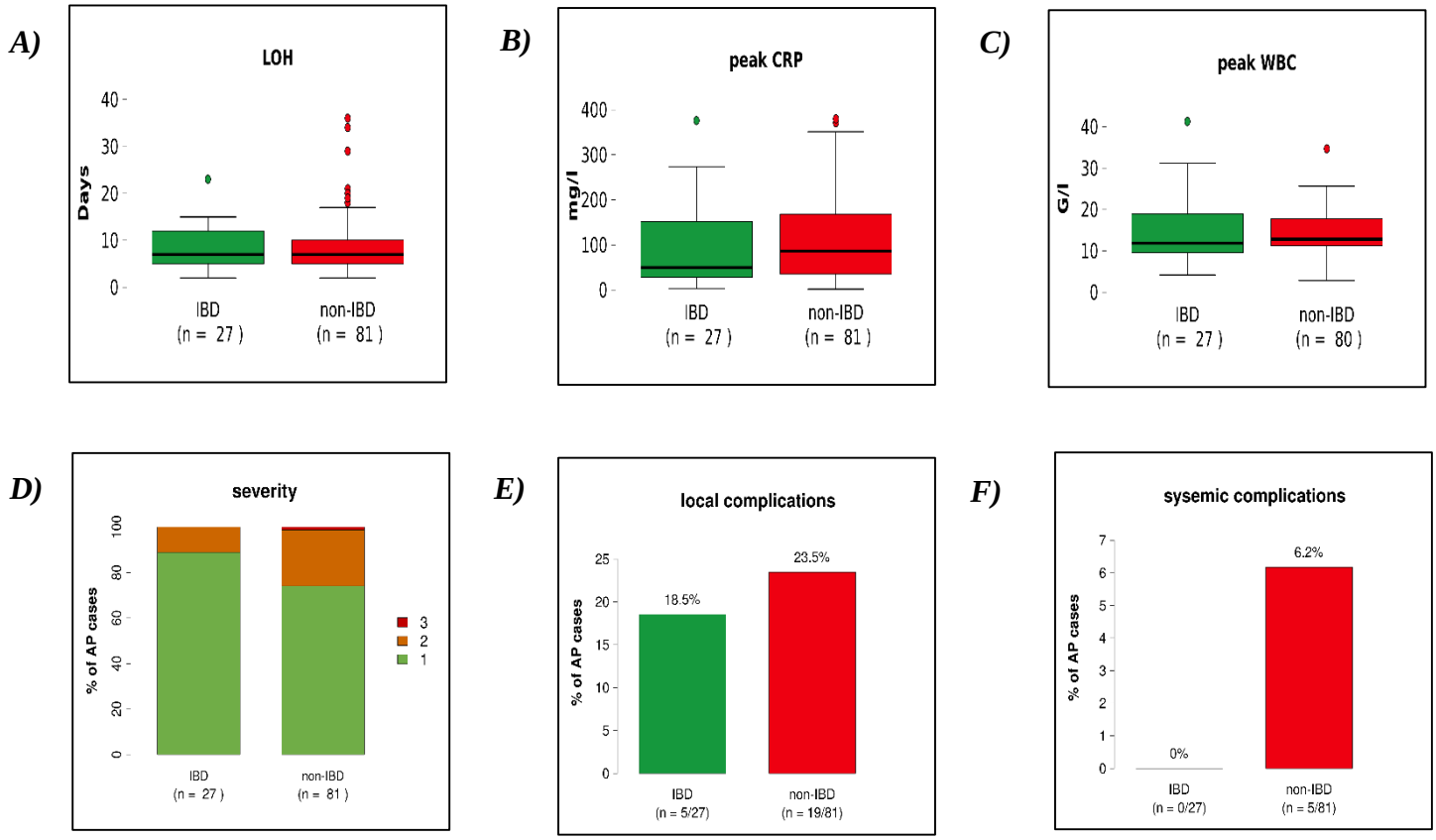


Figure 3 Main results of severity indicators between inflammatory bowel disease (IBD) vs. non-IBD groups

A) length of hospitalization (LOH, p=0.677); ***B)*** peak C-reactive protein (CRP, p=0.239); ***C)*** peak white blood cells (WBC, p=0.432); ***D)*** severity (p=0.384); ***E)*** local (p=0.790) and ***F)*** systemic (p=0.328) complications

N numbers (n) indicate the total number of cases in each group

Figure 4 **Main results of therapy received between inflammatory bowel disease (IBD) vs. non-IBD groups**

A) antibiotic (p=0.642); ***B)*** analgesic (p=0.020) treatment

N numbers (n) indicate the total number of cases in each group

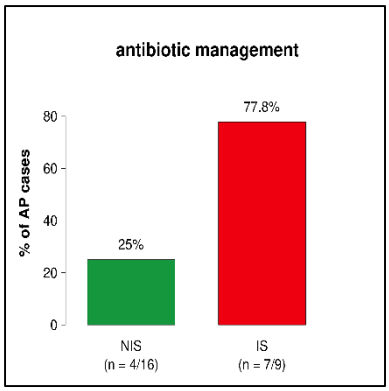


Figure 5 Main results of therapy received between patients on immunosuppressed and non-immunosuppressed therapy

antibiotic management between IS and NIS patients, p=0.017

N numbers (n) indicate the total number of cases in each group

Supplementary table 1.A Quality of data analyzed in inflammatory bowel disease (IBD) and non-IBD

	EPIDEMIOLOGY, ETIOLOGY	OVERALL	UPLOADED DATA	%
1	Age	108	108	100
2	Gender	108	108	100
3	BMI	108	103	95
4	Etiology	108	108	100
5	Smoking habits	108	108	100
6	Drinking habits	108	108	100
	Average uploaded data	648	643	99

	SYMPTOMS AND EXAMINATIONS ON ADMISSION	OVERALL	UPLOADED DATA	%
9	Imaging	108	98	91
10	Imaging results: pancreatic structure	108	90	83
11	Imaging results: ascites	108	76	70
12	bedside index of severity in acute pancreatitis score (BISAP)	108	58	54
	Average uploaded data	432	322	75

	LABORATORY PARAMETERS	OVERALL	UPLOADED DATA	%
13	Amylase	108	104	96
14	Lipase	108	90	83
15	Procalcitonin	108	32	30
16	C-reactive protein	108	95	88
17	Peak C-reactive protein	108	108	100
18	White blood cell count	108	88	81
19	Peak white blood cell count	108	107	99
20	Platelets	108	84	77
21	Creatinine	108	98	90
	Average uploaded data	972	806	83

	INPATIENT TREATMENT	OVERALL	UPLOADED DATA	%
22	Antibiotic treatment	108	91	84
23	Analgesia	108	94	87
24	Intensive care unit treatment	108	98	90
	Average uploaded data	324	283	87

	OUTCOMES	OVERALL	UPLOADED DATA	%
25	Local pancreatic complications	108	108	100
26	Systemic pancreatic complications	108	108	100
27	Length of hospitalization	108	108	100
28	Severity (mild/moderately severe/severe)	108	108	100
29	Mortality	108	108	100
	Average uploaded data	540	540	100
	TOTAL	**2916**	**2594**	**89**

Supplementary table 1.B Quality of data analysed in inflammatory bowel disease patient group

	TYPE AND LOCALIZATION OF IBD	OVERALL	UPLOADED DATA	%
1	Type of IBD (CD or UC)	27	27	100
2	CD localization	27	13	48
3	UC localization	27	11	40
	Average uploaded data	81	51	63

	IBD MANAGEMENT AND DISEASE HYSTORY	OVERALL	UPLOADED DATA	%
4	Types of IBD medication	27	26	96
5	Number of immunosuppressed patients	27	26	96
6	Previous intestinal surgery	27	26	96
7	Current disease activity	27	27	100
	Average uploaded data	108	105	97

	COMORBIDITIES	OVERALL	UPLOADED DATA	%
8	Other comorbidities	27	27	100
9	Other drug treatment	27	27	100
	Average uploaded data	54	54	100
	TOTAL	**243**	**210**	**86**

IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis

Supplementary table 2. Median and IQR values of the parameters analyzed

		IBD patients	*matched controls*
prognostic parameters	**CRP, median (IQR)**	21.2 (8.2-36.9)	14.1 (4.9-39.2)
	WBC, median (IQR)	11.4 (8.6-16.8)	12.5 (9.3-16.4)
	serum creatinine, median (IQR)	78.5 (62.0-87.0)	73.5 (62.8-88.0)
severity indicators	**LOH, median (IQR)**	7.0 (5.0-12.0)	7.0 (5.0-10.0)
	peak CRP level, median (IQR)	49.8 (28.4-152.3)	86.7 (35.4-168.2)
	peak WBC level, median (IQR)	11.82 (9.6-18.9)	12.9 (11.2-17.8)

IBD: inflammatory bowel disease; CRP: C-reactive protein; WBC: white blood cells; LOH: length of hospitalization

Supplementary table 3 **Main results of prognostic parameters, severity indicators, and inpatient treatment in the inflammatory bowel disease subgroups analyzed**

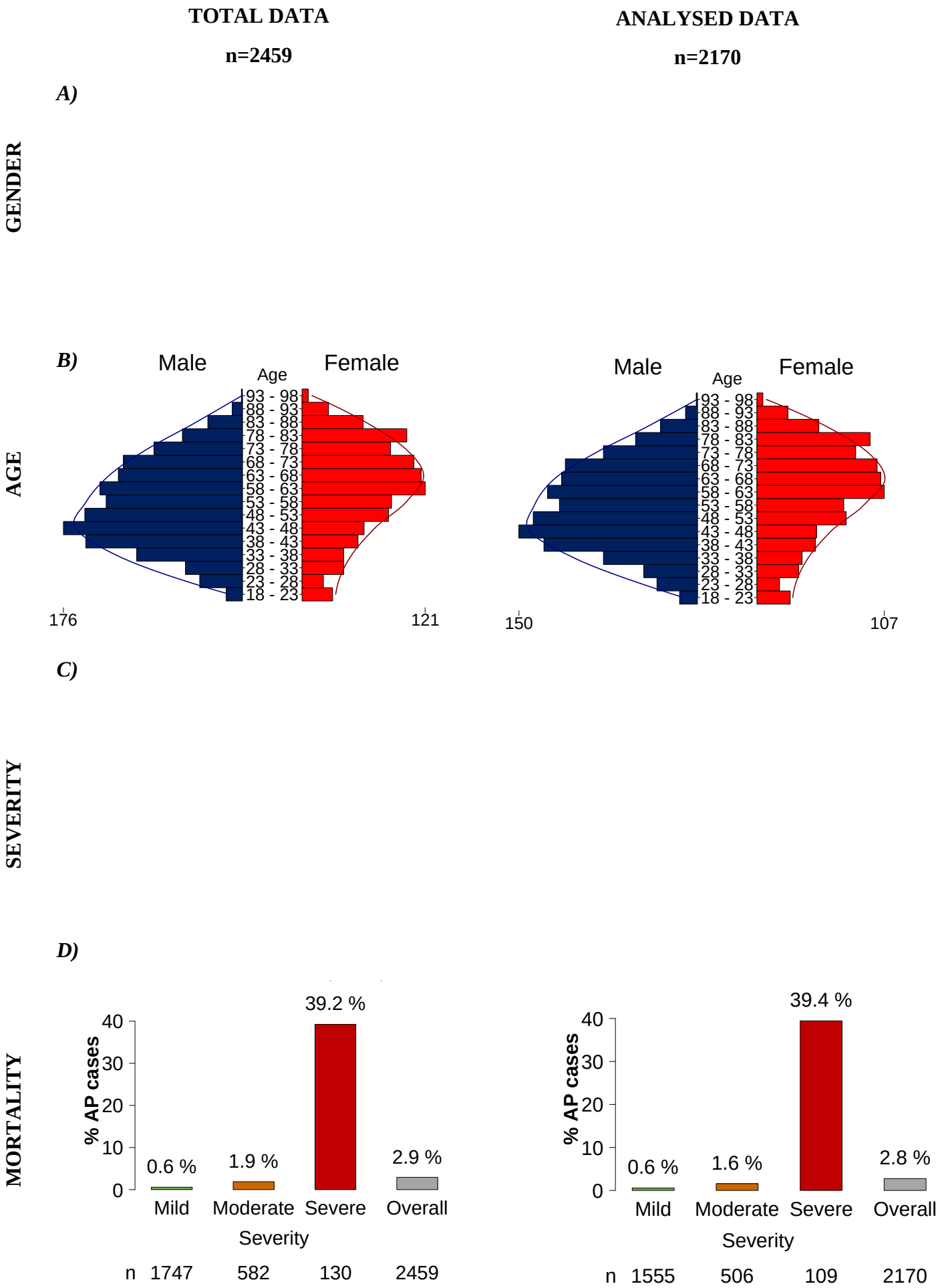
		IBD subgroups		
		CD vs. UC patients	**IS vs. NIS patients**	**patients with active vs. inactive disease**
prognostic parameters	**CRP (*p*)**	0.306	0.192	0.226
	WBC (*p*)	0.959	**0.007**	0.073
	serum creatinine (*p*)	0.608	0.137	0.027
	alcohol consumption (*p*)	0.695	0.098	0.683
	smoking (*p*)	1.000	1.000	1.000
	on admission pancreatic structure (*p*)	0.688	1.000	1.000
	presence of ascites (*p*)	1.000	1.000	0.511
	BISAP (n)	BISAP 0: 3 CD, 0 UC BISAP 1: 4 CD, 2 UC BISAP 2: 1 CD, 0 UC	BISAP 0: 3 IS, 6 NIS BISAP 1: 1 IS, 5 NIS BISAP 2: 0 IS, 1 NIS	BISAP 0: 0 active, 4 inactive BISAP 1: 2 active, 4 inactive BISAP 2: 0 active, 1 inactive
severity indicators	**LOH (*p*)**	0.807	0.301	0.694
	peak CRP level (*p*)	0.685	0.181	0.548
	peak WBC level (*p*)	0.650	0.051	0.256
	local complications (*p*)	1.000	0.591	0.342
inpatient treatment	**antibiotic treatment (*p*)**	0.713	**0.017**	0.113
	analgesic treatment (*p*)	1.000	0.429	1.000

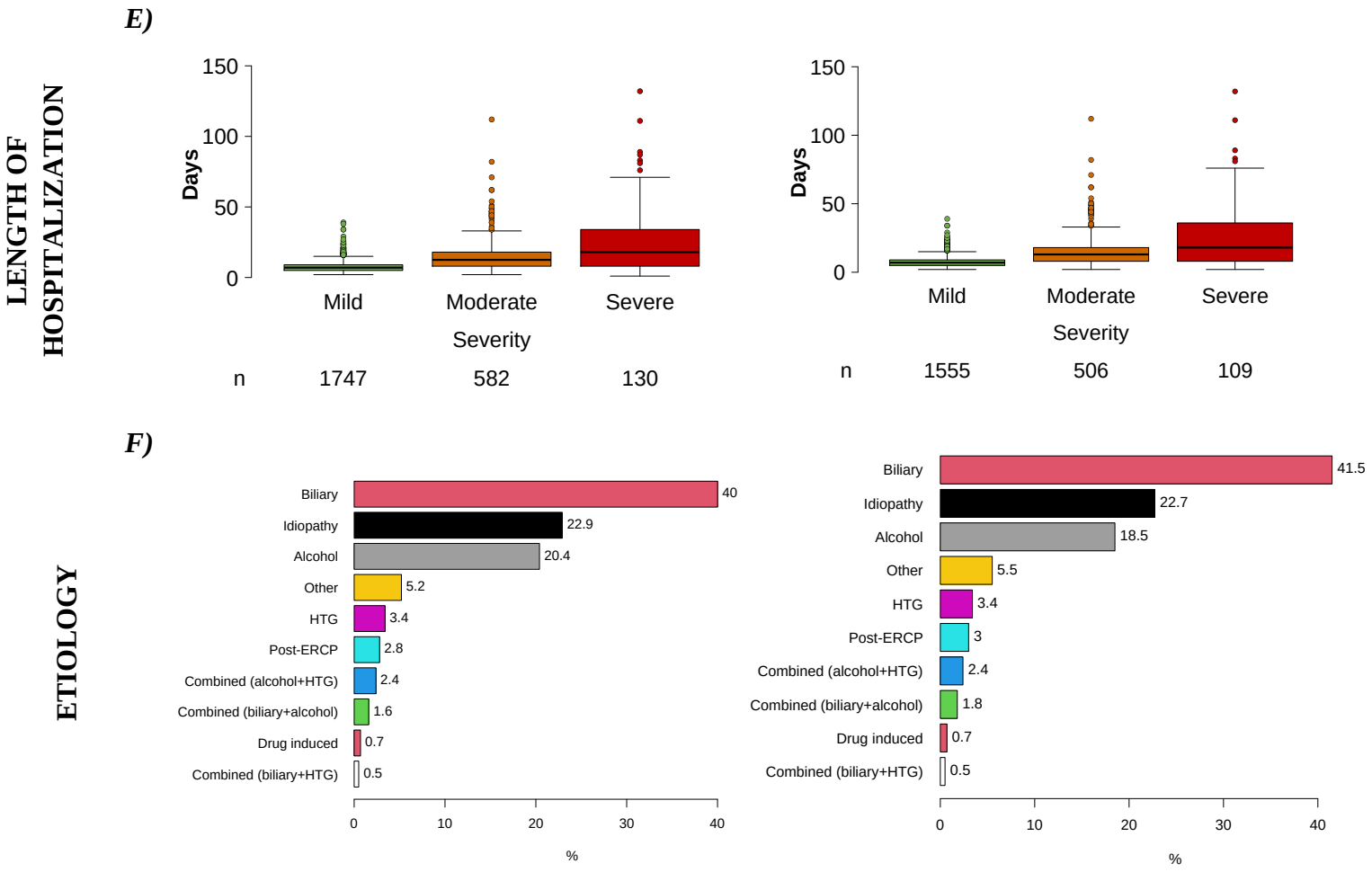
IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IS: immunosuppressed; NIS: non-immunosuppressed; CRP: C-reactive protein; WBC: white blood cells; BISAP: bedside severity index of acute pancreatitis; LOH: length of hospitalization

N numbers (n) indicate the total number of cases

Statistically significance ($p < 0.05$) results are marked with bold

Supplementary Figure 1

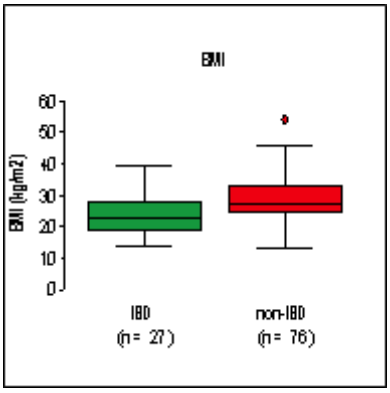




Supplementary Figure 1. Representativity analyses of enrolled patients (n = 2170) compared to the whole cohort (n = 2459)

A) gender distribution of AP cases (p=0.7353); ***B)*** age distribution of AP cases in males and females (p=0.2621); ***C)*** severity distribution of AP cases (p=0.8710); ***D)*** mortality of AP cases in the different severity groups (p=0.8071); ***E)*** length of hospitalization of AP cases in the different severity groups (p=0.5114); ***F)*** etiology distribution of AP cases (p=0.7654)

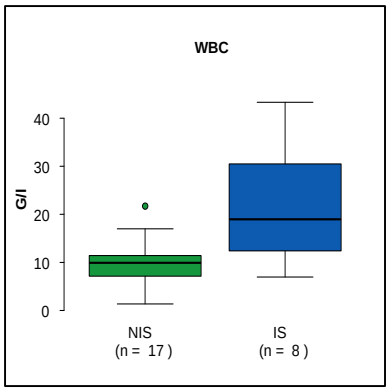
N numbers (n) indicate the total number of cases in each group



Supplementary figure 2 Body mass index results in the IBD and non-IBD populations

body mass index (BMI; p=0.001)

N numbers (n) indicate the total number of cases in each group



Supplementary figure 3 Main results of on-admisson white blood cell level between patients on immunosuppressed and non-immunosuppressed therapy

white blood cells (WBC, *p=0.007*)

N numbers (n) indicate the total number of cases in each group

Inflammatory bowel disease does not alter the clinical features and the management of acute pancreatitis: A prospective, multicentre, exact-matched cohort analysis

Short title: Inflammatory bowel disease and acute pancreatitis

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List of abbreviations

AP	acute pancreatitis
BISAP	bedside index of severity in acute pancreatitis
CRP	C-reactive protein
CD	Crohn's disease
IAP	International Association of Pancreatology
APA	American Pancreatic Association
IBD	inflammatory bowel disease
IS	immunosuppressed
IQR	interquartile range
LOH	length of hospitalization
NIS	non-immunosuppressed
RR	relative risk
SD	standard deviation
UC	ulcerative colitis
WBC	white blood cells

Abstract

Objective and aims: Acute pancreatitis in inflammatory bowel disease occurs mainly as an extraintestinal manifestation or a side effect of medications. We aimed to investigate the prognostic factors and severity indicators of acute pancreatitis and the treatment of patients with both diseases.

Design: We performed a matched case-control registry analysis of a multicentre, prospective, international acute pancreatitis registry. Patients with both diseases were matched to patients with acute pancreatitis only in a 1:3 ratio by age and gender. Subgroup analyses were also carried out based on disease type, activity, and treatment of inflammatory bowel disease.

Results: No difference in prognostic factors (laboratory parameters, bedside index of severity in acute pancreatitis, imaging results) and outcomes of acute pancreatitis (length of hospitalization, severity, and local or systemic complications*)* were detected between groups. Significantly lower analgesic use was observed in the inflammatory bowel disease population. Antibiotic use during acute pancreatitis was significantly more common in the immunosuppressed group than in the non-immunosuppressed group ($p=0.017$). However, none of the prognostic parameters or the severity indicators showed a significant difference between any subgroup of patients with inflammatory bowel disease.

Conclusion: No significant differences in the prognosis and severity of acute pancreatitis could be detected between patients with both diseases and with pancreatitis only. The need for different acute pancreatitis management is not justified in the coexistence of inflammatory bowel disease, and antibiotic overuse should be avoided.

Keywords: acute pancreatitis, inflammatory bowel disease, antibiotics, disease management

What is already known on this topic

- the courses and therapy of acute pancreatitis in patients with inflammatory bowel disease do not differ from the general population
- the acute inflammation of the pancreas may complicate the course of inflammatory bowel disease
- prompt identification of the aetiology and management of pancreatitis is essential to avoid further complications in both pancreatitis and inflammatory bowel disease

What this study adds

- the prognostic parameters of acute pancreatitis did not differ between patients with or without inflammatory bowel disease
- severity parameters of acute pancreatitis did not show significant differences between patients with or without inflammatory bowel disease
- the need for analgesia was significantly lower in patients with both diseases, and the antibiotic use was significantly higher in the immunosuppressed subgroups of patients with inflammatory bowel disease

How this study might affect research, practice or policy

- overuse of antibiotics in the treatment of acute pancreatitis should be avoided as there is no benefit
- antibiotics are not required in immunosuppressed patients with inflammatory bowel disease
- our findings should be analysed in more extensive prospective cohort studies of patients with IBD, with different therapeutic regimens and disease activity.

Introduction

Inflammatory bowel diseases (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic gastrointestinal conditions characterized by relapsing and remitting patterns. Various extraintestinal manifestations with 6 to 47% frequency may also occur, such as arthropathies, erythema nodosum, episcleritis, primary sclerosing cholangitis, and, less frequently, lung, heart, or pancreatic involvement.[1] Due to the increasing incidence of IBD,[2] disease-related complications, e.g., pancreatic manifestations, will also occur more frequently.[3] Possible pathological changes in the pancreas can range from innocent elevation of pancreatic enzymes to more severe disorders,[4] such as acute, chronic, autoimmune pancreatitis, and exocrine dysfunction.[5,6] In a recent meta-analysis by Pedersen *et al.*, patients with CD had a higher incidence of acute pancreatitis (AP) than those with UC, but both were higher than the general population (relative risk [RR]=3.62, 95%CI: 2.99-4.38, p=0.001; RR=2.24, 95%CI: 1.85-2.71, p=0.001, respectively).[7]

The first association between IBD and AP was reported by Ball *et al.*, in 1950, in an autopsy study.[8] Further studies have since reported strong associations between IBD and AP.[9] To date, several possible correlations between IBD and AP have been investigated,[3] including AP as an extraintestinal manifestation and the effect of various IBD drugs,[10] as well as well-known general etiological factors of AP.[9] According to the literature, the most common causes of AP in patients with IBD are choledocholithiasis and drugs.[9,11,12] Drugs are classified into definite, probable, and questionable categories based on their ability to induce AP.[13] Among the medications used in patients with IBD, 5-aminosalicylic acids[14,15] and azathioprine were associated definitely,[12,16-19] while metronidazole and corticosteroids were found probably to be associated with drug-induced AP.[6,20] Although corticosteroids are listed as possible causes of AP; a recent meta-analysis has shown the potential benefits of steroids in the coexistence of severe AP and IBD flares.[21] In addition, combination therapy with tumor necrosis factor-α inhibitors appears to be associated with a reduced risk of AP in patients taking mesalamine, thiopurines, or both.[22] In contrast to the potential benefits of tumor necrosis factor-α inhibitors, another biological agent, vedolizumab, may be associated with an increased risk of AP in adults and children.[23,24]

To the best of our knowledge, the courses and therapy of AP in patients with IBD do not differ from the general population.[3,6] However, the acute inflammation of the pancreas may complicate the course of IBD, so prompt identification of the aetiology and management of pancreatitis is essential to avoid further complications in both pancreatitis and IBD.[6,25] Proper management of AP and IBD is necessary to minimize the length of

hospitalization (LOH), thereby also reducing the economic burden.[26-28] In case of suspicion of drug-induced AP, withdrawal of the drug is mandatory.[6]

Because of the increased incidence and heterogeneous etiological factors of AP in patients with IBD, several studies[12,24,25,29-31] and reviews evaluated their association from different perspectives.[3,9,20,32,33] However, a pancreatic registry has never been used to analyse the characteristics of AP in patients with IBD and to correlate the clinical parameters of AP between patients with or without IBD. In the present study, we collected information from the Hungarian Acute Pancreatitis Registry on patients with both AP and IBD and analysed their data compared to the AP population without IBD and in subgroups of IBD. We aimed to investigate differences in prognostic factors, severity indicators, and drug use between patients with AP or those with co-existing AP and IBD.

Methods

The Hungarian Acute Pancreatitis Registry received ethical approval from the Scientific and Research Ethics Committee of the Medical Research Council (22254e1/2012/EKU) in 2012, and all patients analysed provided written informed consent. In the registry, a four-tier quality control system was applied to ensure data quality, described in detail in a previous publication from the registry.[34,35] The study protocol conforms to the ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in a prior approval by the institution's human research committee. This cohort study follows the STROBE statement for observational cohort studies.[36]

Design, setting, and participants

Adult patients (over 18 years of age) with AP were consecutively involved in this international, multicentre Hungarian Acute Pancreatitis Registry operated by the Hungarian Pancreatic Study Group (HPSG) between 2012 and 2020. Registry-based, exact-matched cohort analyses were performed from a database of 2,459 patients at a 1:3 match ratio. The IBD subjects were patients with both AP and IBD, and the non-IBD ones were patients with AP without IBD. Non-IBD subjects were selected based on exact gender and age data compared to IBD participants. The nationality of patients in both groups was Hungarian.

Data sources and outcomes

Diagnoses of AP and IBD were made according to current guidelines of the International Association of Pancreatology/American Pancreatic Association (IAP/APA), which states that AP requires two of the following three criteria: lipase or amylase levels three times the upper limit of normal, physical symptoms consistent with pancreatitis, and imaging findings. The European Crohn's and Colitis Organisation, and the European Society of Gastrointestinal and Abdominal Radiology. [37,38]

Patients were followed daily during their hospitalization for AP, and their detailed data were collected into an electronic database (e.g., baseline demographics, disease characteristics, and outcome variables). Additional information on IBD was collected from the hospitals' electronic medical records. Disease activity was determined by the Crohn's disease activity index (CDAI) for CD and the Mayo score for UC at the time of admission with AP.[39,40] Based on the pharmacological treatment of IBD used during the AP episode, patients were

classified as immunosuppressed (IS; intravenous or oral steroids, immunomodulatory, and biological therapy) and non-immunosuppressed (NIS; rectal steroid, budesonide, 5-aminosalicylic acids) patients.

From the electronic database, 29 variables of each AP case and additional 9 variables representing IBD were collected in our cohort. (Supplementary Table 1. A, B) The severity of AP, local complications, and organ failure were categorized according to the modified Atlanta criteria.[41]

Our outcomes included the examination of prognostic parameters of AP in the IBD and non-IBD patient groups (laboratory parameters [on admission C-reactive protein /CRP/, white blood cells /WBC/, creatinine, procalcitonin] and imaging results [abnormal pancreatic structure, ascites], bedside index of severity in acute pancreatitis /BISAP/, smoking and drinking habits),[42] severity indicators (severity, mortality, LOH, local and systemic complications, peak level of CRP and WBC, intensive care treatment), and applied therapy during hospital stay (need for antibiotics, analgesics).

Study size and statistical analyses

A total of 2,459 AP cases were collected prospectively with daily follow-up in the registry. 2,170 discharge files were uploaded and read by DD and PS to avoid information bias, check comorbidities, and search for missing information about IBD. Patients were followed up until the end of their hospitalization. Patients were excluded from the corresponding analyses in the case of missing data.

Before the detailed analyses, representativeness analyses were performed to investigate selection bias. Descriptive statistics on cohort characteristics were also carried out. Central tendencies (median and mean) and measures of dispersion (interquartile range [IQR] standard deviation [SD], range) were calculated for continuous variables, whereas incidence was determined for categorical ones. Below, the median with IQR is used because of the non-normal distribution of the data. The control subjects were precisely matched by gender and age in a 1:3 ratio. Firstly, all statistical analyses comparing IBD and non-IBD populations were performed with the controls randomly selected in a 1:1 ratio to obtain detailed results with *p* values. In case of missing data, the participant was excluded from that specific analysis.

Secondly, subgroups of IBD were compared as well, based on disease type (CD vs. UC), immunosuppression therapy (IS vs. NIS), and disease activity (clinical relapse vs. clinical remission).

Depending on the data distribution, Wilcoxon-Mann-Whitney was used for the continuous variables and Fisher's exact test or the chi-square test for the categorical ones. A *p*-value less than 0.05 (< 0.05) was defined as statistical significance. All calculations were performed with R statistical language (R version 4.1.0, R Core Team, Vienna, Austria, 2021).[43]

Results

Study population

Of the 2,459 enrolled patients with AP, 289 were excluded due to missing final reports. Further investigations were performed on 2,170 patients. The representativeness analysis demonstrated that our cohort presents the same epidemiological (age, gender, body mass index, aetiology) and major outcome distribution (severity, mortality, LOH) as the total cohort. Thus, our cohort population describes a general AP population. (Supplementary Figure 1)

A detailed review of 2,170 final medical AP records confirmed 27 cases of IBD as an IBD population. (Figure 1) The non-IBD population without the diagnosis of IBD was precisely matched by age and sex from the Hungarian Acute Pancreatitis Registry (n=81). All patients were followed until discharge. The patients involved may have had other comorbidities; they were not involved in the description and analysis due to their significant variances. The baseline characteristics of the IBD and non-IBD groups are summarized in Table 1. A. Twenty-nine AP episodes were diagnosed in 27 patients with IBD, including 14 patients with CD and 13 with UC. Twelve of the 27 patients were in relapse, while 15 patients were in remission during the AP episode. Nine patients were identified with IS and 17 with NIS treatment. Between the patients with IBD and without IBD, body mass index was significantly lower in the IBD population (p=0.001). (Supplementary Figure 2) The baseline clinical features of IBD at the time of AP are summarized in Table 1. B.

Table 1.A Baseline characteristics of the inflammatory bowel disease (IBD) and non-IBD groups

Characteristics		*IBD patients (n = 27)*	*non-IBD patients (n = 81)*	p-values
Age, median (IQR)		42 (32-62.5)	42 (32-62.5)	/
Gender, male, n (%)		15 (55.6)	45 (55.6)	/
Drinking habits: drinker, n (%)		9 (33.3)	39 (48.2)	p_1=0.57; p_2=0.17; p_3=0.57
Smoking habits: smoker, n (%)		9 (33.3)	24 (29.6)	p_1=1.00; p_2=1.00; p_3=0.35
Aetiology of acute pancreatitis, n (%)	*Alcohol*	1 (3.7)	14 (17.3)	/
	Biliary	5 (18.5)	36 (44.4)	
	Drug induced	8 (29.6)	0 (0.0)	
	Combined	0 (0.0)	9 (11.1)	
	Hypertriglyceridemia	0 (0.0)	3 (3.7)	
	Idiopathic	7 (25.9)	16 (19.8)	
	Other	6 (22.2)	3 (3.7)	
Severity of acute pancreatitis, n (%)	*Mild*	24 (88.9)	60 (74.0)	p_1=0.69; p_2=0.06; p_3=0.48
	Moderate	3 (11.1)	20 (24.7)	
	Severe	0 (0.0)	1 (1.2)	
Laboratory parameters, median (IQR)	*Amylase*	579 (317.5-1028.5)	701 (268-1536)	p_1=0.53; p_2=0.68; p_3=0.1
	Lipase	1349 (914-1995)	1439 (600.3-3419.8)	p_1=0.89; p_2=0.81; p_3=0.6
	Platelets	243.50 (180-311.5)	268 (225.5-338.3)	p_1=0.33; p_2=0.40; p_3=0.6

IBD: inflammatory bowel disease

Table 1.B Baseline characteristics of IBD patients

Characteristics			*IBD patients (n = 27)*
Type of IBD, n (%)	*CD*		14 (51.9)
	UC		13 (48.1)
Disease localization (Montreal classification), n (%)	*CD*	*ileum*	7 (53.8)
		ileocolonic	4 (30.8)
		colon	2 (15.4)
	UC	*left sided colitis*	4 (36.4)
		proctitis	4 (36.4)
		pancolitis	3 (27.2)
IBD treatment, n (%)	*Azathioprine*		5 (19.2)
	Biological therapy		1 (3.9)
	5-ASA		20 (76.9)
	Steroid		6 (23.0)
Immunosuppressed patients, n (%)			9 (34.6)
	Azathioprine		3 (33.3)
	Steroid		4 (44.4)
	Azathioprine + steroid		1 (11.1)
	Azathioprine + biological therapy		1 (11.1)
Activity of IBD, n (%)	*Patient in remission*		15 (55.6)
	Patient in relapse		12 (44.4)
Previous intestinal surgery, n (%)			4 (15.4)
Comorbidities, n (%)			17 (62.9)
Concomitant treatments, n (%)			18 (66.7)

IBD: inflammatory bowel disease; CD: Crohn's disease, UC: ulcerative colitis

Main results of prognostic parameters

Eight parameters (on-admission CRP, WBC, and serum creatinine, BISAP, smoking and drinking habits, imaging results of the pancreas, presence of ascites) were examined to investigate any difference between AP patients with or without IBD and between subgroups of the IBD population. Due to the high proportion of missing data, procalcitonin levels could not be examined. Of the 27 patients with IBD, procalcitonin was measured in only nine patients on admission, with a mean of 0.107 ng/ml (min-max: 0.02-0.29).

None of the laboratory parameters of prognostic factors showed significant differences between IBD and non-IBD cases (CRP: p=0.297; WBC: p=0.538; serum creatinine: p=0.794*).* (Figure 2. A-C) No differences were observed between the two groups in BISAP scores, pancreatic structure, or the presence of ascites (BISAP: p=0.832; pancreas structure: p=1.000; ascites p=0.203). (Figure 2. D-F) Almost the same proportion of patients from the two groups had BISAP 0 and 1 at diagnosis (56.2% vs. 52.4% and 37.5% vs. 28.6%, respectively), but fewer patients from the IBD group had BISAP 2 (6.2% vs. 14.3%). BISAP 3 occurred only in the IBD group (4.8%), and no BISAP 4 and 5 were observed. The rate of current alcohol consumption and smoking showed no differences either (33.3% vs. 48.1%; p=0.263, and 33.3% vs. 29.6%; p=0.810, respectively). (Supplementary Table 2)

On admission, WBC levels in NIS patients were significantly lower than IS patients. (p=0.007) (Supplementary Figure 3) Further prognostic parameters analysed did not show significant differences between subgroups of patients with IBD. See other results detailed in Supplementary Table 2.

Main results of the severity indicators

Six parameters (LOH, peak level of CRP and WBC, severity, local and systemic complications) were analysed to reveal differences between groups. None of the patients with IBD and AP died during follow-up, and none of the IBD patients were treated in the intensive care unit for AP; thus, mortality and intensive care treatment were not included in the analyses.

LOH (p=0.677*)* and peak levels of CRP (p=0.239) and WBC (p=0.432*)* did not show significant differences between the IBD and non-IBD populations. (Figure 3. A-C) There was no significant change in the severity of AP (p=0.384). However, the rate of moderate and severe cases was higher in the non-IBD group (mild: 89% vs. 74%, moderate: 11% vs. 24.7%, and severe: 0% vs. 1.2%). (Figure 3.D) None of the local or systemic

complications of AP showed a significant alteration between the groups examined (p=0.790 and p=0.328, respectively). (Figure 3. E-F, Supplementary table 2)

The three different IBD subgroup analyses demonstrated no significant alteration in the severity indicators. (Supplementary Table 3)

Inpatient treatment

Of the 27 cases in the IBD group, eight drug-induced AP were registered. The putative aetiological factors, azathioprine in three, and 5-aminosalicylic acids in five AP episodes, were stopped immediately.

Antibiotic treatment and pain management were studied to establish differences between groups and subgroups. Antibiotic treatment showed no significant differences (46.2% vs. 40.0%; p=0.642), but significantly more patients from the non-IBD group required analgesics than patients in the IBD group (55.6% vs. 80.6%; p=0.020). (Figure 4. A-B)

Antibiotic use was significantly higher in the IS group compared to the NIS group (p=0.017), although a clear indication (e.g., fistula or abscess) was not present. At the same time, there was no significant difference in antibiotic use between CD vs. UC and between patients with active or inactive disease. (Figure 5, Supplementary Table 3) No significant differences were found in antibiotics or analgesics use between patients with CD or UC and patients with active or inactive disease. (Supplementary Table 3)

Discussion

IBD is a chronic gastrointestinal condition characterized by intermitting relapsing and remitting patterns and the potential for extraintestinal manifestations. Due to the increasing incidence of IBD,[2] several cases of AP have been reported in association with IBD worldwide.[3,7] Since the association was first described in 1950, a number of strong correlations have been revealed. The most common aetiological factors for AP in patients with IBD are choledocholithiasis and IBD medications.[9,11,12] Appropriate treatment of AP, especially drug-induced pancreatitis in patients with IBD is crucial to avoid further complications and relapse after drug-withdrawal.

In this present study, we evaluated a cohort of patients with IBD in the Hungarian Acute Pancreatitis Registry and assessed in detail the differences of AP in patients with and without IBD. Due to the heterogeneity of aetiology, these factors were not evaluated and compared between groups. Although type 2 autoimmune pancreatitis can occur in association with IBD, this aetiology was not observed in our small cohort.

Firstly, several prognostic factors examined in our cohort did not reveal significant differences between AP patients with or without IBD. Our results are in line with the results of Jasdanwala *et al*., where the severity and prognosis of AP in patients with CD did not differ from the general population.[20] While, in other studies, the incidence of AP was higher in patients with CD,[12,26,44] nearly the same number of patients with CD or UC with the same characteristics of AP were registered in our cohort. Similar to the literature data, no differences in smoking and drinking habits were observed between our cohort's IBD and non-IBD populations.[13] The relationship between AP and disease activity remains questionable, as this previously released issue could not be confirmed in our cohort.[12] Although WBC levels were significantly higher in the IS subgroup than the NIS group, this difference was likely due to the low number of patients involved (alpha type error).

Secondly, various factors characterizing the severity of AP were examined, where no significant differences were found between groups and subgroups. In accordance with the literature data, the majority of AP cases from the IBD population were mild, with a small percentage being moderately severe.[12,20,30] No systemic complication was observed in our cohort, as in cases of mild to moderate AP, sterile inflammation remains in the pancreas.[25] No mortality was observed in IBD patients. As Alexoff *et al.* had previously reported, we found no longer hospital stays in patients with IBD and AP.[26]

Thirdly, the need for analgesia was significantly lower in the IBD population; we hypothesize that chronic illnesses may result in a higher pain tolerance threshold. Antibiotic use was significantly higher in the IS group than in the NIS group of patients with IBD. WBC counts on admission were significantly higher in the IS group,

but any parameter indicating a more severe form of pancreatitis or signs of IBD relapse cannot explain this clinical decision. We hypothesize that increased caution in patients taking IS may contribute to this significantly higher antibiotic use. In a review, Fousekis *et al*. stated that treatment of AP should not be different in patients with different comorbidities.[6] In laboratory or clinically unjustified cases, unreasonable drug therapy should be considered to reduce hospital costs, as the treatment of both AP and IBD is associated with high health care costs.[26] Moreover, unwarranted antibiotic therapy in IBD can lead to dysbiosis, which can cause acute flare-ups or affect the subsequent disease course of IBD.

According to the previous reviews, treatment of AP should not be modified in patients with IBD unless a disease flare-up coincides.[6,9] Treatment of moderate to severe AP in the setting of a flare of IBD may be challenging due to the conflicting literature on the effects of steroids on AP. According to Ramos et al., steroids may increase the risk of pancreatic necrosis and fluid collection.[9] In contrast, a recent meta-analysis revealed that steroid therapy does not worsen but improvs the outcome of severe AP.[45] In the case of flare-up of IBD, in addition to the known treatment of AP, the use of biologics instead of steroids, especially infliximab, has been considered.[6]

Although, ongoing concomitant treatment of IBD should not be stopped to avoid intestinal complications or flare-ups, but in cases where the IBD drug used is the putative aetiology of AP, immediate discontinuation is recommended because the generally mild, drug-induced AP responds rapidly to drug withdrawal.[12,29] Due to the high risk of recurrence of proven azathioprine or mercaptopurine induced AP, rechallenge of these drugs is contraindicated even at low doses.[46,47] A possible secondary expert opinion of the previously suspected triggering etiological factor may be necessary in the case of a chronic condition requiring drug treatment before the withdrawal of effective therapy.

Our present study has several strengths. This prospective cohort study collected daily clinical data with standardized question forms, thus minimizing information bias. Due to the study design, the changes between diagnosis and discharge provided better evidence of the results. We analysed the cohort's main epidemiological and outcome parameters compared to the whole cohort to minimize selection bias. Exactly matched control selection was used to compensate for the possible biases resulting from the small number of IBD cases.

Our cohort analysis has several limitations that suggest a careful interpretation of the results. As with most other cohort analyses, our clinical research question was defined post hoc, so not all aspects of AP-IBD could be investigated. The validity of our evaluation and results may be impaired by the small sample size of IBD patients. In addition to the small sample size, a lack of data allowed no further analyses. Patients excluded due to

missing final reports may contribute to selection bias. Furthermore, the analyses of the IBD subgroups were not feasible in the case-control design due to the low number of cases. There was a considerable variation in the aetiology of AP, so subgroup analyses based on this and further analyses of how aetiology may impact the course of AP were not feasible in the present study.

Conclusion

In summary, our results did not confirm any differences in the prognosis and severity of AP between patients with IBD and the general AP population, regardless of disease type and activity.[3] Overuse of antibiotics was observed in patients on immunosuppressive therapy, probably due to elevated levels of on admission WBC, platelet, and peak WBC counts. Based on our previous cohort analysis,[48] in agreement with the F17–18 recommendations in the IAP/APA guidelines,[37] overuse of antibiotics in the treatment of AP should be avoided as there is no benefit. Due to the same severity and prognostic results observed in the IBD population, antibiotics are not required in IS patients. Our findings should be analysed in more extensive prospective cohort studies of patients with IBD, with different therapeutic regimens and disease activity.

Authors' contribution

Conceptualization: DD, PS, methodology: NF, AV, PS, review of final reports: DD, PS; statistical analyses: NF, AV; writing-original draft preparation: DD, SP; visualization: DD, AV; review: BE, AP, ASz, PH and funding acquisition: AP, PH, PS

Data availability statement

The data underlying this article are available in the article and its online supplementary material.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Legend of tables and figures

Tables

Table 1 **Baseline characteristics of the inflammatory bowel disease (IBD) and non-IBD groups (A); Disease characteristics in the IBD group (B)**

Figures

Figure 1 **Flowchart of patient selection**

Figure 2 **Main results of prognostic parameters between inflammatory bowel disease (IBD) vs. non-IBD groups: C-reactive protein (A); white blood cells (B); serum creatinine (C); bedside index of severity in acute pancreatitis (D); pancreas structure (E); ascites (F); alcohol consumption (G) and smoking (H)**

Figure 3 **Main results of severity indicators between inflammatory bowel disease (IBD) vs. non-IBD groups: length of hospitalization (A); peak C-reactive protein (B), peak white blood cells (C), severity (D); local (E) and systemic (F) complications**

Figure 4 **Main results of therapy received between inflammatory bowel disease (IBD) vs. non-IBD groups: antibiotic (A) and analgesic (B) treatment**

Figure 5 **Main results of antibiotic therapy received between patients on immunosuppressed and non-immunosuppressed therapy**

Supplementary material

Supplementary tables

Supplementary Table 1 **Quality of data analysed in inflammatory bowel disease (IBD) and non-IBD (A) and IBD (B) patient groups**

Supplementary Table 2 **Median and interquartile range (IQR) values of the parameters analysed**

Supplementary Table 3 **Main results of prognostic parameters, severity indicators, and inpatient treatment in the inflammatory bowel disease subgroups analysed**

Supplementary figures

Supplementary Figure 1	**Representativity analyses of enrolled patients (n = 2170) compared to the whole cohort (n = 2459): gender distribution of acute pancreatitis cases (A); age distribution of acute pancreatitis (AP) cases in males and females (B); severity distribution of AP cases (C); mortality of AP cases in the different severity groups (D); length of hospitalization of AP cases in the different severity groups (E); aetiology distribution of AP cases (F)**
Supplementary Figure 2	**Body mass index results in the inflammatory bowel disease and non-IBD populations**
Supplementary Figure 3	**Main results of on-admission white blood cell levels between patients on immunosuppressed and non-immunosuppressed therapy**