sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 76 (2022), No. 5/6 (740/741), pp. 608–617.

DOI: 10.2478/prolas-2022-0094

Original Paper

BURDEN OF EXTRAINTESTINAL MANIFESTATIONS AND COMORBIDITIES IN TREATED AND UNTREATED ULCERATIVE COLITIS AND CROHN'S DISEASE: A LATVIAN NATIONWIDE PRESCRIPTION DATABASE STUDY 2014–2019

Irēna Teterina[1,#], Viktorija Mokricka[2,4], Eva Petrošina[3], and Juris Pokrotnieks[2,4]

[1] Faculty of Pharmacy, Rīga Stradiņš University, 13 Pilsoņu Str., Rīga, LV-1002, LATVIA

[2] Pauls Stradiņš Clinical University Hospital, 13 Pilsoņu Str., Rīga, LV-1002, LATVIA

[3] Faculty of Medicine, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[4] Faculty of Medicine, Rīga Stradiņš University, 14 Baložu Str., Riga, LV-1048, LATVIA

[#] Corresponding author, irena.teterina@rsu.lv

Communicated by Dainis Krieviņš

Inflammatory bowel diseases (IBD) are frequently accompanied by extraintestinal manifestations (EIMs) due to systemic autoimmune processes, which are important in the management of IBD patients and their long-term outcomes. The aim of the study was to determine the occurrence of EIMs comorbidities and their burden in IBD patients, based on the Latvian nationwide reimbursed prescription database from 2012 till 2019. Incident Crohn's disease (CD) and ulcerative colitis (UC) patients between 2014 and 2018 were matched on age and sex with non-treated IBD controls and followed up until 2019. EIMs were selected based on a previously used methodology and grouped into organ systems. The cohort was tested for differences in the timing and occurrence of EIMs, as well as overall cumulating disease burden. The study population included 187 CD and 1137 UC patients. Higher prevalence of EIMs was observed in untreated IBD patients, whereas in the treated IBD patient group prevalence remained numerically similar. Among treated patients, the most common EIMs affected cardiovascular, hepatopancreatobiliary, endocrine, musculoskeletal, respiratory, and the skin and intestinal tract systems, where 28.4–79.9% of IBD patients experienced these EIMs for the first time before their IBD diagnosis. The treated female IBD patients tended to have higher frequency of EIMs compared to male patients. The overall comorbidity burden trend increased with time. The study provides evidence that treated IBD patients have lower risk for EIMs/comorbidities compared to untreated IBD patients.

Keywords: *inflammatory bowel disease, National Health Services and Central Statistics Bureau databases, epidemiology, autoimmune disease.*

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing–remitting, inflammatory condition of the gastrointestinal tract, which consists of Crohn's disease (CD) and ulcerative colitis (UC) (Ananthakrishnan 2015). The pathogenesis of these illnesses remains unclear, but current evidence suggests a synergic effect of genetic, environmental, and health-related factors (Mahid *et al.*, 2006; Baumgart *et al.*, 2011; van Limbergen *et al.*, 2014; Ruel *et al.*, 2014; Ananthakrishnan 2015).

IBD affects both sexes at similar rates, with incidence peaking in younger adults (Molodecky *et al.*, 2012). 25–30% of IBD patients suffer from one or more extraintestinal manifestations (EIMs) (Su *et al.,* 2002; Lakatos *et al.,* 2003). Ac-

cording to the latest findings, up to 50% of IBD patients will experience at least one EIM (Harbord *et al.*, 2016). Extraintestinal symptoms can be divided in two groups: EIMs and extraintestinal complications (Vavricka *et al.*, 2015). In IBD, EIM most frequently affects joints (peripheral and axial arthropathies), the hepatopancreatobiliary system (primary sclerosing cholangitis), the skin (psoriasis, erythema nodosum, pyoderma gangrenosum, oral aphthous ulcers), and the eyes (episcleritis, uveitis). Less frequently, IBD affects lungs, heart and the vascular system and is challenging to detect due to an asymptomatic disease course. Patients may be affected by more than one EIM (Rogler *et al.*, 2021). Extraintestinal complications are caused by the disease itself and include anaemia, malabsorption, osteoporosis, peripheral neuropathies, kidney stones, gallstones, and drug-related side effects (Danese *et al.,* 2005; Cosnes *et al.,* 2011). Like other immune-mediated diseases, including psoriasis and rheumatoid arthritis, IBD is associated with several comorbid conditions, and is defined as an association of a group of diseases with a given condition (Boehncke, 2018; Kaine *et al.*, 2018). However, the magnitude of comorbid disease impact on IBD patients' treatment and outcome not always is taken into consideration (Munoz *et al.*, 2011).

The prevalence and incidence of EIMs is dependent on the types of EIMs. A more stringent definition of EIMs was suggested by the European Crohn's and Colitis Organization's (ECCO) working group: "An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD" (Hedin *et al.*, 2019). Patients with IBD usually require life-long monitoring and therapy, which significantly impacts their quality of life and has considerable implications for the health system. IBD-associated EIMs and comorbidities accumulate over time, and it is important to acknowledge the local situation for proper healthcare (HC) resource planning and allocation, as well for measurement of HC system efficiency over time in disease and comorbidity management. The first steps for understanding the overall incidence and prevalence of IBD in Latvia were already attempted (Mirzajanova *et al.*, 2020). The incidence of EIMs and comorbidities in IBD patients in Latvia remains unclear and lack of data was already highlighted previously (Krustins and Pokrotnieks, 2014). Our study sought to investigate the burden of IBD comorbidities in Latvia and changes between 2014 and 2019.

MATERIALS AND METHODS

The study included all patients who received reimbursed medicine therapy for a IBD diagnosis in the period from 2014 till 2018, and their EIMs/comorbidities, followed up until the end of 2019.

This study was based on a population of incident patients with CD or UC in the period of 2014–2018 and followed up until 2019, who were identified in the Latvian National Health Service (NHS) database on reimbursed medical service, including medicines. The NHS database allows identification and linkage of all state covered health services (including reimbursed medicines) for the Latvian population based on unique person identifiers and diagnosis codes according to International Classification of Diseases 10th edition (ICD-10), which additionally contains information on patient sex, age, and site of residency. Collection of reimbursed medicine prescription data in digital form started in 2012, which was selected as a starting point of data collection in this study. The following INNs were reimbursed: Azathioprinum, Dexamethasonum, Mercaptopurinum, Mesalazinum, Budesonidum, Methylprednisolonum, Prednisolonum, Sulfasalazinum, and biological therapy: Adalimumabum, Infliximabum (both from 2015), Ustekinumabum (from 2018 CD, and from 2021 UC), and Vedolizumabum (from 2019) (NHS, no year). The private healthcare system in IBD was assumed to constitute up to 40% of the treated patients until 2018, as all medicines, including biologics for IBD patients were reimbursed at a 75% level by the state. Starting from 2018, all IBD patients received 100% state coverage for reimbursed medicines.

Incident patients with CD (ICD-10 code K50) and UC (ICD-10 code K51) were identified in the reimbursed medicines database as individuals with at least five reimbursed medicines prescriptions for K50 and K51, and with at least three months of treatment for this diagnosis. It is important to note that more loose criteria for selection of IBD patients also were tested, considering at least two reimbursed medicines (McAuliffe *et al.*, 2015), but this did not affect the results significantly. A relative control group was created from patients having only one prescription for IBD diagnosis, as these were patients who were not adherent to IBD therapy or initially misdiagnosed with IBD. Even though some studies consider one prescription as being enough for assigning a patient to compliant IBD groups (Freeman *et al.*, 2021), in this study, we chose a more stringent selection criteria for IBD patients. The study groups would allow comparison between treated IBD patients and non-treated (due to low adherence to therapy, poor access to therapy due to co-payment, or not fully confirmed) IBD patients. To limit the analysis to incident cases, the patients were excluded if they had a reimbursed medicine for CD/UC in the "wash-out" period of 2012–2013. It was considered that a two-year wash out period was sufficient, as only 5-aminosalicylic acid (5-ASA), azathioprine and 6 mercaptopurine (6-MP) therapy was reimbursed till 2018, and according to literature data, 91% of UC patients with 5-ASA therapy relapse within 24 months (Chapman *et al.*, 2020). Also, 5-ASAs failed to demonstrate superiority compared to no treatment (Gjuladin-Hellon *et al.*, 2019). Cumulative risk of relapse with time after withdrawal of azathioprine monotherapy in both CD and UC is about 30% after two years and 50–75% after five years (Doherty *et al.*, 2018). However, discontinuation of azathioprine therapy after achieving

remission in moderate to severe forms of CD and UC is not a common clinical practice in Latvia. The incidence dates for patients were defined as the first reimbursed prescription date with CD/UC in the period from 2014 to 2018.

Some patients with CD may have initially been misdiagnosed with UC, and vice-versa. Therefore, in this study, patients were assigned to UC or CD groups based on the latest diagnosis.

For each identified CD case (and every 2 CD cases), one control patient was randomly selected from the non-IBD patient cohort (those who had only one IBD prescription in the period from 2014 to 2018 for 5-ASA preparations) and matched on January 1st in the year of IBD diagnosis on age and sex.

The selected EIMs and comorbidities for this study included 51 different diagnoses divided into seven classes, based on a previously published methodology (Vadstrup *et al.*, 2020): the musculoskeletal system, the skin and intestinal tract systems, the hepatopancreatobiliary system, the ocular system, the endocrine system, neurological diagnosis, and the respiratory system. Renal system comorbidities were not analysed in this study, as no reimbursed medicines were available for corresponding diagnosis of calcium oxalate stones (N20). Recently, cardiovascular disease, malignancies, osteoporosis, and psychiatric disorders were identified as the major comorbidities among patients with rheumatoid arthritis and psoriasis (van Onna *et al.*, 2016). Similarly, several other comorbidities, such as metabolic syndrome and neurological diseases, have been described as important emerging conditions among the autoimmune disease patient population (Turreson, 2016; Strober *et al.*, 2018). Therefore, the original methodology was complemented with twenty-nine diseases of interest that were analysed and reported separately. Criteria of grouping of selected EIMs and comorbidities and corresponding ICD codes from reimbursed medicines database are provided in Supplementary materials, Table S1. Additionally, to understand the sex differences and burden of comorbidities in treated IBD patients, sex prevalence and the Charlson Comorbidity Index were calculated at the time of diagnosis and at the end of the follow up period in 2019 (Quan *et al.*, 2005). The frequency of EIMs/comorbidities was calculated by diagnosis class (e.g., neurological system) and for selected comorbidities (e.g., thyroid disorders) separately for CD/UC patients and controls. Statistics of EIMs and comorbidities was estimated through odds ratios (ORs) and 95% CI confidence intervals by an unadjusted logistic regression and test for significant differences between patient and the relative control groups. In addition, a separate analysis on EIMs and comorbidities in the period before and after diagnosis of IBD was conducted, as EIMs and comorbidities may occur before as well as after the CD/UC diagnosis. Statistical analysis was conducted in MS Office Excel 2019 and RStudio version 2019.09.1.

Ethical approval. Approval from the Rīga Stradiņš University Research Ethics Committee was received. Anonymised data without contact or active participation of research subjects were used. Individuals are not identifiable. The requested data were reviewed and approved by the NHS.

RESULTS

For the period of eight years (1 January 2012 till 31 December 2020), 6173 unique patients including paediatric patients were treated with reimbursed medication for CD and UC indications. After case selection, 187 CD (age 10–88 years) and 1137 UC (age 1–95) incident patients were included in the analysis (for case selection algorithm see Figure 1). 359 (18.7%) patients had fluctuations in IBD diagnosis, of which 90 % of prescriptions with different diagnosis were issued by general practitioners. Study population characteristics are shown in Table 1.

EIMs/comorbidity incidences among cases and controls during 2014–2018 are presented in Supplementary materi-

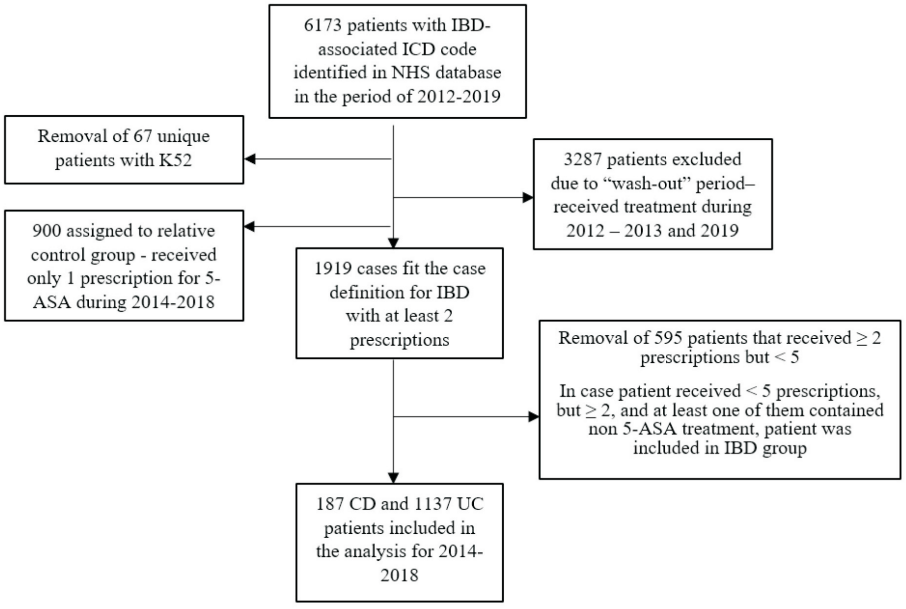

Fig. 1. Flowchart of ascertainment of inflammatory bowel disease (IBD) cases in Latvia from 2012 to 2019. CD, Crohn's disease; UC, ulcerative colitis NHS, Latvian National Health Service.

Table 1. Characteristics of the patient population

Age at diagnosis	Sex	CD, N (%) = 187	UC, N (%) = 1,137
0–18 years	Female	4 (2.1%)	24 (2.1%)
	Male	16 (8.6%)	24 (2.1%)
19–30 years	Female	15 (8.0%)	88 (7.7%)
	Male	32 (17.1%)	87 (7.7%)
31–40 years	Female	14 (7.5%)	110 (9.7%)
	Male	20 (10.7%)	141 (12.4%)
41–50 years	Female	12 (6.4%)	68 (6.0%)
	Male	7 (3.7%)	93 (8.2%)
51–60 years	Female	14 (7.5%)	86 (7.6%)
	Male	7 (3.7%)	73 (6.4%)
61–70 years	Female	19 (10.2%)	94 (8.3%)
	Male	6 (3.2%)	54 (4.7%)
Over 70 years	Female	14 (7.5%)	143 (12.6%)
	Male	7 (3.7%)	52 (4.6%)
	Sex total		
	Female	92 (49.2%)	613 (53.9%)
	Male	95 (50.8%)	524 (46.1%)

CD, Crohn's disease; UC, ulcerative colitis

als, Table S2. For most of EIMs/comorbidities, a significantly larger share of relative controls experienced a comorbidity. From the full list of EIMs and comorbidities, higher prevalence was observed in both untreated control groups — UC (72.9%) vs CD (63.6%), whereas in the IBD patient group, prevalence remained similar — 58.5% and 54%, respectively.

Prevalence of EIMs/comorbidities in IBD patients and untreated controls. When comparing CD patients and their matched controls, almost none of comorbidities that were analysed in scope of this study were statistically significantly higher compared to confirmed CD patients, except in the respiratory system (see Supplementary materials, Table S2). However, untreated CD patients had by 9.6% more comorbidities than in treated CD patients. Of diseases of special interest, in most cases the difference was not statistically significant, with numerical trend resembling the picture observed in UC. In the treated CD patient group, psychiatric disorders were less prevalent than in the untreated CD control patient group, 3.7% vs 9.6, OR 0.37 (95% CI 0.14, 0.86). Chronic ischemic heart disease was observed at a higher incidence rate in the untreated CD control group than in the treated CD patient group (12.8% vs 5.9%, respectively). Conjunctivitis also was observed more frequently in the control group (see Supplementary materials, Table S2).

For UC patients, more pronounced differences were observed (see Table 2), where multiple diagnoses had lower risk in the treated UC patient population compared with the non-treated UC control (musculoskeletal, ocular, respiratory systems). Regarding diseases of special interest, the lowest observed risk in treated UC patients was found for rheumatoid arthritis (OR 0.28, 95% CI 0.16–0.49), conjunctivitis (OR 0.10; 95% CI 0.02–0.30), and chronic ischemic heart disease (OR 0.36, 95% CI 0.26–0.48). Lower prevalence with significantly smaller risk in the treated UC control group was seen for cardiovascular disease — 45.6% vs 56.2% in the untreated UC group (incl. angina pectoris, arrhythmias, heart failure and hypertensive disorders), (OR 0.66, 95% CI 0.53–0.80). Other significant comorbidities with lower risk in treated UC patients were psychiatric disorders (OR 0.53, 95% CI 0.37–0.78), asthma (OR 0.70, 95% CI 0.52–0.94), cerebrovascular diseases (OR 0.46, 95% CI 0.33–0.64) and thyroid disorders (OR 0.71, 95% CI 0.51–1.00).

The distribution of EIMs/comorbidities among cases and controls during 2014–2018, independent of the time of the diagnosis, is presented in Table 2 for the seven organ systems. The most common EIMs/comorbidities among untreated CD patients was the respiratory system (14.4% vs 7.5%). For treated UC controls, a statistical difference was observed for the musculoskeletal system with OR 0.54 (95% CI 0.40–0.73), ocular system OR 0.10, (95% CI 0.02–0.30) and respiratory system OR 0.68, (95% CI 0.51–0.91). Risk of any comorbidity for treated UC patients was by 14.4% lower than in untreated UC patients.

Table 3 shows experienced EIMs/comorbidities before and after IBD diagnosis. The majority of EIMs/comorbidities

Table 2. Share of population experiencing EIMs or other comorbidities in the period of 2014–2019 by diagnosis class among 187 patients with CD and 1137 patients with UC in Latvia and their matched controls

	CD, % of patients in each group				UC, % of patients in each group			
	CD, n = 187	Control, n = 187	OR	95% CI	UC, n = 1,137	Control, n = 568	OR	95% CI
Hepatopancreatobiliary system	6.4%	8.0%	0.79	0.35, 1.73	6.5%	8.3%	0.77	0.53, 1.13
Endocrine system	13.4%	17.6%	0.72	0.41, 1.26	20.5%	23.4%	0.84	0.66, 1.08
Musculoskeletal system	12.3%	13.9%	0.87	0.47, 1.59	9.7%	16.5%	0.54*	0.40, 0.73
Neurological	1.6%	1.6%	1.00	0.18, 5.46	2.3%	2.5%	0.93	0.49, 1.84
Ocular system	0.0%	2.1%	-	-	0.3%	2.6%	0.10*	0.02, 0.30
Respiratory system	7.5%	14.4%	0.48*	0.24, 0.93	11.9%	16.5%	0.68*	0.51, 0.91
Skin and intestinal tract systems	8.6%	4.3%	2.09	0.90, 5.28	4.0%	5.1%	0.78	0.49, 1.27
Any EIM	54.0%	63.6%	0.67	0.44, 1.01	58.5%	**72.9%**	0.52*	0.42, 0.65

*Statistically significant, $p < 0.05$, **"-"** is due to no patients in one of comparable groups; CD, Crohn's disease; UC, ulcerative colitis

Table 3. Share of population experiencing first EIMs/comorbidities in the period of 2014–2019 by class of diagnosis, stratified by time of IBD diagnosis among 187 patients with CD and 1137 patients with UC in Latvia and their matched controls

Crohn's disease	CD, n = 187	Control, n = 187	OR	95% CI	CD, n = 187	Control, n = 187	OR	95% CI
	Before CD diagnosis				After CD diagnosis			
Cardiovascular diseases	29%	40%	0.61*	0.39, 0.93	12%	5.3%	2.48*	1.18, 5.61
Hepatopancreatobiliary system	2.1%	3.7%	0.56	0.15, 1.89	4.3%	4.3%	1.00	0.36, 2.77
Malignancies	0%	0%	-	-	0.5%	0%	-	-
Endocrine system	9.6%	14%	0.66	0.34, 1.24	3.7%	3.7%	1.00	0.34, 2.98
Musculoskeletal system	6.4%	9.1%	0.69	0.31, 1.47	5.9%	4.8%	1.24	0.50, 3.14
Neurological	0.5%	1.6%	0.33	0.02, 2.60	1.1%	0%	-	-
Ocular system	0%	1.6%	-*		0%	0.5%	0.00	-
Psychiatric disorders	2.1%	4.8%	0.43	0.12, 1.35	1.6%	4.8%	0.32	0.07, 1.10
Respiratory system	7.0%	10%	0.66	0.31, 1.37	0.5%	4.3%	0.12*	0.01, 0.67
Skin and intestinal tract systems	5.3%	1.6%	3.47*	1.04, 15.6	3.2%	2.7%	1.21	0.36, 4.25
Ulcerative colitis	UC, n = 1.137	Control, n = 568	OR	95% CI	UC, n = 1.137	Control, n = 568	OR	95% CI
	Before UC diagnosis				After UC diagnosis			
Cardiovascular diseases	36%	48%	0.62*	0.50, 0.76	9.1%	7.9%	1.17	0.82, 1.70
Hepatopancreatobiliary system	1.8%	4.0%	0.45*	0.24, 0.81	4.7%	4.2%	1.11	0.68, 1.84
Malignancies	< 0.1%	0.5%	0.17	0.01, 1.30	0.2%	0%	-	-
Endocrine system	14%	18%	0.71*	0.55, 0.94	6.7%	5.1%	1.33	0.87, 2.10
Musculoskeletal system	4.7%	11%	0.40*	0.27, 0.58	4.9%	5.5%	0.90	0.58, 1.42
Neurological	1.2%	1.2%	1.00	0.41, 2.65	1.1%	1.2%	0.85	0.34, 2.31
Ocular system	0.2%	1.9%	0.09*	0.01, 0.33	< 0.1%	0.7%	0.12*	0.01, 0.84
Psychiatric disorders	2.2%	4.8%	0.45*	0.26, 0.78	3.4%	5.3%	0.64	0.39, 1.04
Respiratory system	7.7%	9.2%	0.82	0.58, 1.18	4.2%	7.4%	0.55*	0.36, 0.85
Skin and intestinal tract systems	2.4%	2.5%	0.96	0.51, 1.90	1.7%	2.6%	0.63	0.32, 1.26

*Statistically significant, $p < 0.05$, **"-"** is due to no patients in one of comparable groups; CD, Crohn's disease; UC, ulcerative colitis

were identified before IBD diagnosis. The only comorbidities that appeared more frequently after IBD diagnosis were those affecting the hepatopancreatobiliary system, with similar results between CD and UC patients. Untreated IBD patients generally had higher rates of comorbidities than treated patients. In treated CD patients, cardiovascular diseases were found in 29.0% of cases compared with 40% in untreated CD controls, ocular system disorders were not found in treated patients compared to three in controls (1.6%), skin and intestinal tract manifestations were found in 10 patients (5.3%) compared with 3 cases (1.6%) in untreated controls, resulting in OR 3.50 (95% CI 1.04–15.6). After CD diagnosis most notable differences were observed in cardiovascular diseases, where treated patients had higher OR 2.50 (95% CI 1.18–5.61), but had lower risk for respiratory system diseases (OR 0.12, 95% CI 0.01–0.67). Treated UC patients had lower risk of having an EIM before UC diagnosis, compared to their untreated controls — lower risk of ocular system comorbidities by 92%, musculoskeletal by 60%, hepatopancreatobiliary system and psychiatric disorder comorbidities by 55%, cardiovascular by 38% and endocrine by 29%.

5.3% (n = 10) of all CD treated patients and 2.4% (n = 27) of all treated UC patients experienced EIMs/comorbidities in the skin and intestinal tract systems before their IBD diagnosis, and after IBD diagnosis (3.2% (n = 6) and 1.7% (n = 19), respectively). The respective values for EIMs/comorbidities in untreated CD and UC patients before IBD diagnosis varied between 1.6% to 2.5%, and after IBD diagnosis — 2.7% and 2.6%, respectively. 2.1% (n = 4) of all treated CD patients and 1.8% (n = 20) of UC patients experienced EIMs/comorbidities in the hepatopancreatobiliary system before their IBD diagnosis, compared with untreated controls — 3.7% (n = 7) and 4.0% (n = 23). After IBD diagnosis, treated and untreated patient risks were similar for both CD and UC patients.

Time from IBD incidence to first time experiencing EIMs/comorbidities. All patients who experienced EIMs/comorbidities were stratified according to time from CD/UC diagnosis to the first experience of each EIM/comorbidity (Supplementary materials, Table S3). Among treated patients with the most common EIMs/comorbidities (in the cardiovascular system, the hepatopancreatobiliary system, endocrine system, musculoskeletal system, respiratory system, and the skin and intestinal tract systems), 33.0–72.0% of CD patients and 28.4–79.9% of UC patients experienced these EIMs/ comorbidities for the first time before their IBD diagnosis. Notable differences were observed in psychiatric disorders — observed in 92.9% of CD patients vs 39% of treated UC patients. In CD patients, un-

treated controls more frequently than treated patients had the following EIMs/comorbidities prior to diagnosis — cardiovascular system, hepatopancreatobiliary system, musculoskeletal system, neurological and ocular (more frequently by 13.2–66.7%), but less frequently — psychiatric and skin and intestinal tract comorbidities (less frequently by 21.2–42.9%).

Comorbidities that were not identified before IBD diagnosis usually appeared within the first year from IBD diagnosis and the minority were found in the following years.

Comorbidity sex difference in treated IBD patients. In treated female CD and UC patients, higher frequency in following comorbidities was observed, compared with male patients: cardiovascular, endocrine, musculoskeletal systems, osteoporosis, and lipoprotein metabolism disorders. In general, treated male patients had lower risk for any EIM/comorbidity compared to female patients in CD and UC, with (OR 0.25 (95% CI 0.14–0.46) and (OR 0.70 (95% CI 0.55–0.89), respectively. Interesting differences were observed in the treated UC patient group, where female patients had higher frequencies of depression (7.0% vs 4.0%), neurological disorders (3.1% vs 1.3%), rheumatoid arthritis (2.4% vs 1.0%) and thyroid disorders (13.0% vs 2.3%), than male patients. The only identified disease where male patients had higher risk than female UC patients was COPD with (OR 2.17 (95%CI 1.05–4.73) (Supplementary materials, Table S4).

Charlson Comorbidity Index (CCI) in treated IBD patients. The majority of IBD patients had a low comorbidity burden with CCI before IBD diagnosis, where 82% of CD and 76% of UC patients had CCI = 0. The increase in CCI over time was by 0.26 points (SD 0.67) for CD patients and by 0.28 points (SD 0.75) in UC patients. Mean values of CCI for the whole duration of follow up were higher for UC patients: 0.78 points (SD 1.29) vs CD 0.60 points (SD 1.11) (Supplementary materials, Table S5.1 and S5.2).

DISCUSSION

The aim of our study was to quantify the proportion of EIMs/comorbidities in treated and untreated CD and UC patients, as well as to identify sex differences in treated IBD patients and overall comorbidity burden. EIMs and comorbidities included in this study were based on a previously used methodology in Denmark (Valdstrup *et al.*, 2020), with modification for Latvia. The created list was not exhaustive and focused on EIMs/comorbidities of interest in the Latvian population.

According to ECCO, approximately 50% of IBD patients have at least one EIMs, which can be present before IBD diagnosis. This is in line with our study findings —— treated IBD patients had EIMs in 54.0–58.0% of cases, compared to untreated IBD controls (63.6–72.7%). The most common EIMs/comorbidities in CD and UC patients were observed in endocrine, musculoskeletal, and respiratory systems, with higher risk in the untreated IBD control group. The findings are slightly different compared to other studies, as hepatopancreatobiliary and skin/intestinal tract comorbidities were less prevalent. This can be explained by fragmented patient care and lack of centralised IBD care units, which would coordinate IBD patients in the HC system and ensure multidisciplinary assessment and treatment. Development of a dedicated IBD care unit with availability of a multidisciplinary team (including Rheumatologist, Dermatologist, Pathologist, Ophthalmologist, Nutrition specialist, and Psychologist) and clear system of patient referral could be a possible solution. Each EIM affects patient quality of life and may lead to disability. Some EIM, such as venous thromboembolism and primary sclerosing cholangitis, may be life-threatening (Harbord *et al.*, 2016).

Female sex has been reported as a risk factor for EIMs (Wagtmans *et al.*, 2001), and our study confirms this idea.

In IBD patients, gut-related microvascular inflammation results in diminished vasodilatory capacity and tissue hypoperfusion. Furthermore, persistent inflammation increases the risk of venous and arterial thrombosis at an earlier age (Papa *et al.*, 2008). Several large studies (Yarur *et al.*, 2011; Kirchgesner *et al.*, 2017) found an increased risk of acute arterial events in patients with Crohn's disease and ulcerative colitis, including ischaemic heart disease, cerebrovascular disease, and peripheral artery disease. Our study shows that patients receiving therapy for CD and UC have lower risk for these comorbidities, compared to untreated IBD patients, showing the benefit of IBD treatment for cardiovascular and cerebrovascular comorbidities (Yarur *et al.*, 2011).

Musculoskeletal manifestations are the most common EIMs with prevalence varying between 7–25% (Danese *et al.*, 2005). In a Canadian (UMIBDED) study, ankylosing spondylitis was more common among men, with the highest rate among men with CD (2.7%). In our study the highest rate was observed in the CD group — 1.6%. This difference can be explained by the geographical area and use of different diagnostic criteria.

Reduced bone mineral density and bone fractures are described to be more common among the IBD population, with an estimated frequency for osteoporosis of 14–42% (up to 50%). Compared with controls, the fracture risk for patients with IBD is higher by approximately 40–60% (Schüle *et al.*, 2017). It is affected by disease activity, chronic inflammation, corticosteroids usage, and small bowel involvement or resection (Harbord *et al.*, 2016). Our findings show lower prevalence of osteoporosis in the IBD patient cohort, with 8% in CD and only 0.5–1.8% in UC patients. Regarding sex differences, female patients in both CD and UC had higher prevalence of 10–15% vs male IBD patients with only 1.3–2.1%. The study findings highlight the need for proper attention to bone health and implementation of a screening programme for IBD patients with high risk factors for osteoporosis, and initiation of treatment when necessary.

Analysing results of neurological disorders, overall, no difference between treated and untreated patient cohorts were observed, with slightly higher proportion in UC patients. In comparison, some studies have observed increased incidence of Parkinson's disease (Lin *et al.*, 2016). A systematic review and meta-analysis found that those with IBD and multiple sclerosis have a 50% increased risk of multiple sclerosis or IBD comorbidity, respectively, with no apparent differences between patients with CD or UC (Kosmidou *et al.*, 2017). In a Canadian study, multiple sclerosis was increased in UC (prevalence = 0.54%; PR = 1.9; 95% CI, 1.19–3.03). but not in CD patients, as in our study.

Psoriasis is a chronic systemic immune-mediated disorder affecting approximately 0.5% to 11.4% of adults and approximately 1.4% of children. Patients with psoriasis had 1.70-fold increased odds of CD and 1.75-fold increased odds for UC (Michalek *et al.*, 2017; Yun *et al.*, 2018). According to a large meta-analysis from 93 studies on the prevalence of psoriasis in patients with IBD, prevalence of psoriasis in patients with CD and UC was 3.6% and 2.8%, respectively (Alinaghi *et al.*, 2020). In our study, psoriasis prevalence was 3.3% in the UC group (similar between treated and untreated patients) and 4.3% in treated CD patients (in the untreated group prevalence was lower — 1.3%). A possible explanation for this is that untreated CD patients in general are not compliant not only in IBD, but also in psoriasis treatment, and additionally they might pay less attention to their health and skin condition. The presence of more prevalent psychiatric comorbidities in untreated IBD patient groups can be explained by low adherence and early discontinuation of IBD therapy.

Acute pancreatitis is usually associated with alcohol use, gallstones, hypertriglyceridemia, and drug-related side effects. Chronic pancreatitis (CP) is characterised by the presence of pancreatic duct abnormalities in IBD patients, and in IBD patients can be of autoimmune, idiopathic, with PSH associated and granulomatous origin. CP with pancreatic duct abnormalities have been found in 8% in CD and 16% in UC. The incidence ratio for chronic pancreatitis is higher in the UC group (Harbord *et al.*, 2016). Our findings show that the CP incidence ratio in both diseases is similar: in the CD group incidence is 5.5% compared with the UC group — 5.1%, which may be related with asymptomatic course of the disease.

IBD patients with active complicated disease have higher risk for cancer, where the most common is colorectal cancer (CRC), for which risk increases with age. CRC is the second leading cause of cancer deaths in the world. Current IBD therapies, such as immunomodulators and biological agents may increase the risks of non-Hodgkin's lymphoma (azathioprine/6MP) and both non-melanoma (thiopurines and anti-TNF) and melanoma (anti-TNF) skin cancer among individuals with IBD. A Northern California study reported stable CRC incidence rates among patients with IBD, with a 1.6-fold higher incidence than in the general population (Danese *et al.*, 2005). In our study, patients with a follow up period up to six years (which may not be long enough to capture all cancer related risks), the cancer risk was 2.1% in both treated and untreated CD and 0.5% in treated UC patient vs 1.8% in untreated UC patients, and no sex differences were observed. The difference between treated and untreated UC patients can be partially explained by more frequent visual diagnostic investigations that in treated UC patients, and therefore any changes in colon could be identified and treated earlier.

In general, treated male patients had lower risk for any EIM/comorbidity compared to female patients in CD and UC. This can be explained by the younger male cohort, due to lower average life expectancy in the Latvian male population (70.8 years vs 79.9 years for female patients) (OECD, 2021). The only identified disease where male patients had higher risk than female UC patients was COPD with OR 2.17 (95% CI 1.05–4.73). This may be explained by 3.2 times higher prevalence of smoking in the Latvian male population (38% of total male population are smokers), compared to the female population (SPKC, 2018).

In our study, we found three cases of necrotising vasculitis, all of which were reported in the treated CD patient group. Even though literature reports higher rates of vasculitis in IBD patients (Sy *et al.*, 2016), additional investigation of cases is needed for detailed vasculitis classification and underlying reasons, as this study did not assess effect of received medicines on comorbidities.

Study limitations include case identification algorithm, since it has not been validated in the Latvian patient cohort. It might be that having five prescriptions with therapy duration of at least three months is not enough to distinguish the true IBD patient from a patient with IBD-like symptoms. Additionally, diagnosis could not be verified via endoscopy or radiological investigation, which is necessary to prove the diagnosis of IBD; therefore overestimation of the true IBD population in Latvia is possible. Important consideration when comparing incidence rates of EIMs/comorbidities with other countries is medication reimbursement policy (e.g., cardiovascular disease medicines, antidepressants) in the period of 2014–2019 in Latvia are reimbursed at 50–75% rate, and require out of pocket payments. There could be a proportion of patients that do not receive therapy due to high co-payments, as also highlighted in the WHO report (OECD, 2021). Before 2015, medications for IBD were reimbursed by the state in the amount of 50 or 75%, whereas starting from 2018 some important groups of medications became 100% reimbursed; this year was also highlighted by broader accessibility of biologic therapy. Another limitation of this study is that some important IBD EIMs and comorbidities, such as fistulas and anaemia, could not be assessed, as no reimbursed medicines in Latvia for this diagnosis were available in the period from 2014 to 2018. Additionally, the five-year period might not be long enough to capture all IBD-related EIMc/comorbidities. To our knowledge, this is the first study to report comparisons between treated and non-treated IBD patient populations for prevalence of EIMs/comorbidities in the Baltics. The strengths of our study include wide patient representation

that goes beyond a single centre and is representative of the Latvian IBD patient population. Additionally, the study was designed based on previously published methodology with comparable results. Our study demonstrates that treated IBD patients have lower overall EIM/comorbidity burden by almost 15% and have reduced risk for many known EIMs/comorbidities, which reinforces the role of pharmacologic treatment in management of multi-morbid autoimmune disease patients. Additional studies are needed to evaluate treatment impact and possible connections with EIM and comorbidity development risk.

CONCLUSIONS

This study provides evidence that treated IBD patients have lower risk for EIMs/comorbidities compared to untreated IBD patients. This indicates that IBD treatments are instrumental in controlling IBD patient morbidity and implies common pathogenetic mechanism of IBD and related EIMs/comorbidities. The results suggest diagnostic delay of IBD, and occurrence of known EIMs should trigger additional investigations for early identification of IBD. Additional studies with prospective registries and longer follow up in Latvian and Baltic populations are needed to understand impact of specific pharmacologic treatments and combinations in controlling EIMs/comorbidities. This has implications for both epidemiology and healthcare expenditure planning.

CONFLICT OF INTEREST

Authors received no financial support in development of this study. The study was developed as part of the doctoral thesis of Irēna Teterina (I.T.). I.T., which was an employee of UAB "Johnson&Johnson", Latvian branch. Other authors have no conflict of interest to declare.

SUPPLEMENTARY MATERIALS

Table S1. List of EIMs and other comorbidities included in the analysis. *Table S2.* Share of population experiencing EIMs or comorbidities of special interest in the period 2014–2019 among 187 patients with CD and 1137 patients with UC in Latvia and their matched controls (only statistically significant findings for CD and/or UC presented). *Table S3.* Time from IBD incidence to first time experiencing EIMs/comorbidities in the period 2014–2019 among 187 patients with CD and 1137 patients with UC in Latvia. *Table S4.* Comorbidity gender difference in treated IBD patients in the period 2014–2019 among 187 patients with CD and 1137 patients with UC in Latvia**.** *Table S5.1.* Comorbidity sex difference based on Charlson comorbidity index (CCI) in treated IBD patients in the period 2014–2019 among 187 patients with CD and 1137 patients with UC in Latvia**.** *Table S5.2.* Comorbidity sex difference based on Charlson Comorbidity Index (CCI) in treated IBD patients in the period 2014–2019 among 187 patients with CD and 1137 patients with UC in Latvia.

REFERENCES

Alinaghi, F., Tekin, H. G., Burisch, J., Wu, J. J., Thyssen, J. P., Egeberg, A. (2020). Global prevalence and bidirectional association between psoriasis and inflammatory bowel disease: A systematic review and meta-analysis. *J. Crohn's Colitis*, **14** (3), 351–360.

Ananthakrishnan, A. N. (2015). Epidemiology and risk factors for IBD. *Nature Rev. Gastroenterol. Hepatol.,* **12** (4), 205–217. https://doi.org/10.1038/nrgastro.2015.34.

Baumgart, D. C., Bernstein, C. N., Abbas, Z., Colombel, J. F., Day, A. S., D'Haens, G., Dotan, I., Goh, K. L., Hibi, T., Kozarek, R. A. *et al.* (2011). IBD Around the world: Comparing the epidemiology, diagnosis, and treatment: proceedings of the World Digestive Health Day 2010–Inflammatory Bowel Disease Task Force meeting. *Inflamm. Bowel Dis*., **17** (2), 639–644.

Boehncke, W.-H. (2018). Systemic inflammation and cardiovascular comorbidity in psoriasis patients: Causes and consequences. *Front Immunol*., **9**, 579.

Chapman, T. P., Frias Gomes, C., Louis, E., Colombel, J. F., Satsangi, J. (2020). Withdrawal of 5-aminosalicylates in inflammatory bowel disease. *Alim. Pharmacol. Ther.,* **52** (1), 73–84.

Cosnes, J., Gowerrousseau, C., Seksik, P., Cortot, A. (2011). Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*, **140**, 1785–1794.

Danese, S., Semeraro, S., Papa, A., Roberto, I., Scaldaferri, F., Fedeli, G., Gasbarrini, G., Gasbarrini, A. (2005). Extraintestinal manifestations in inflammatory bowel disease. *World J. Gastroenterol.,* **11** (46), 7227. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4725142/.

Doherty, G., Katsanos, K. H., Burisch, J., Allez, M., Papamichael, K., Stallmach, A., Mao, R., Berset, I. P., Gisbert, J. P., Sebastian, S., Kierkuś, J. (2018). European Crohn's and Colitis Organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J. Crohn's Colitis*, **12** (1), 17–31. https://academic.oup.com/ecco-jcc/article/12/1/17/4060442#107604318.

Freeman, K., Ryan, R., Parsons, N., Taylor-Phillips, S., Willis, B. H., Clarke, A. (2021). The incidence and prevalence of inflammatory bowel disease in UK primary care: A retrospective cohort study of the IQVIA Medical Research Database. *BMC Gastroenterol.,* **21** (1), 1–7. https://academic.oup.com/jcag/article/2/Supplement_1/S17/5153302?login=true.

Fu, Y., Lee, C. H., Chi, C. C. (2018). Association of psoriasis with inflammatory bowel disease: A systematic review and meta-analysis. *JAMA Dermatology*, **154** (12), 1417–1423. DOI: 10.1001/jamadermatol.2018.3631.

Gjuladin-Hellon, T., Gordon, M., Iheozor-Ejiofor, Z., Akobeng, A. K. (2019). Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database of Systematic Reviews*, (6). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008414.pub3/full.

Harbord, M., Annese, V., Vavricka, S. R., Allez, M., Barreiro-de Acosta, M., Boberg, K. M., Burisch, J., De Vos, M., De Vries, A. M., Dick, A. D., Juillerat, P. (2016). The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J. Crohn's Colitis*, **10** (3), 239–254. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957476/.

Hedin, C. R. H., Vavricka, S. R., Stagg, A. J., Schoepfer, A., Raine, T., Puig, L., Pleyer, U., Navarini, A., Van Der Meulen-De Jong, A. E., Maul, J., Katsanos, K. (2019). The pathogenesis of extraintestinal manifestations: Implications for IBD research, diagnosis, and therapy. *J. Crohn's Colitis*, **13** (5), 541–554.

Kaine, J., Song, X., Kim, G., Hur, P., Palmer, J. B. (2018). Higher incidence rates of comorbidities in patients with psoriatic arthritis compared with the

general population using US administrative claims data. *J. Manag. Care Spec. Pharm.,* 24, 1–11.

Kirchgesner, J., Beaugerie, L., Carrat, F., Andersen, N. N., Jess, T., Schwarzinger, M. (2017). Increased risk of acute arterial events in young patients and severely active IBD: A nationwide French cohort study. *Gut*, **67**, 1261–1268.

Kosmidou, M., Katsanos, A. H., Katsanos, K. H., Kyritsis, A. P., Tsivgpoulis, G., Christodoulou, D., Giannopoulos, S. (2017). Multiple sclerosis and inflammatory bowel diseases: A systematic review and meta-analysis. *J. Neurol.,* **264**, 254–259.

Krustins, E., Pokrotnieks, J. (2014). IBD prevalence in Baltic states or just a guessing game? *J. Crohn's Colitis*, **8** (8), 902–902.

Lakatos, L., Pandur, T., David, G., Balogh, Z., Kuronya, P., Tollas, A., Laszlo, L. (2003). Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: Results of a 25-year follow-up study. *World J. Gastroenterol.,* **9**, 2300–2307.

Lin, J.-C., Lin, C.-S., Hsu, C.-W., Lin, C.-L., Kao, C.-H. (2016). Association between Parkinson's disease and inflammatory bowel disease. *Inflamm. Bowel Dis.,* **22**, 1049–1055.

Mahid, S. S., Minor, K. S., Soto, R. E., Hornung, C. A., Galandiuk, S. (2006). Smoking and inflammatory bowel disease: A meta-analysis. *Mayo Clin. Proc*., **81**, 1462–1471.

McAuliffe, M. E., Lanes, S., Leach, T., Parikh, A., Faich, G., Porter, J., Holick, C., Esposito, D., Zhao, Y., Fox, I. (2015). Occurrence of adverse events among patients with inflammatory bowel disease in the HealthCore Integrated Research Database. *Curr. Med. Res. Opin.*, **31** (9), 1655–1664. https://www.tandfonline.com/doi/abs/10.1185/03007995.2015.1065242?journalCode=icmo20.

Michalek, I. M., Loring, B., John, S. M. (2017). A systematic review of worldwide epidemiology of psoriasis. *J. Eur. Acad. Dermatol. Venereol.,* **31** (2), 205–212. https://onlinelibrary.wiley.com/doi/10.1111/jdv.13854.

Mirzajanova, I., Purviņa, S., Pokrotnieks, J. (2020). Incidence and prevalence of Crohn's disease and ulerative colitis (2013–2017) Based on the Latvian Nationwide Medicines Reimbursement Database. In: *Proc. Latvian Acad. Sci. Section B.,* **74** (2), 138–143. https://sciendo.com/pdf/10.2478/prolas-2020-0022.

Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., Benchimol, E. I., Panaccione, R., Ghosh, S., Barkema, H. W., Kaplan, G. G. (2012). Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*, **142**, 46–54. e42; quiz e30.

Nacionālais veselības dienests (2021). Kompensējamie medikamenti. Normatīvo aktu sistēma [National Health Service. Reimbursable drugs. Laws and regulations]. www.vmnvd.gov.lv

OECD (2021). *Health at a Glance 2021: OECD Indicators*. OECD Publishing, Paris. https://doi.org/10.1787/ae3016b9-en.

OECD/European Observatory on Health Systems and Policies (2021). *Latvia: Country Health Profile 2021*. State of Health in the EU. OECD Publishing, Paris. https://doi.org/10.1787/919f55f0-en.

Papa, A., Scaldaferri, F., Danese, S., Guglielmo, S., Roberto, I., Bonizzi, M., Mocci, G., Felice, C., Ricci, C., Andrisani, G., *et al.* (2008). Vascular involvement in inflammatory bowel disease: Pathogenesis and clinical aspects. *Dig. Dis*., **26**, 149–155.

Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., Saunders, L. D., Beck, C. A., Feasby, T. E., Ghali, W. A. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med. Care*, 1130–1139.

Received 6 March 2022
Accepted in the final form 11 April 2022

https://journals.lww.com/lww-medicalcare/Abstract/2005/11000/Coding_Algorithms_for_Defining_Comorbidities_in.10.aspx.

Rogler, G., Singh, A., Kavanaugh, A., Rubin, D. T. (2021). Extraintestinal manifestations of inflammatory bowel disease: Current concepts, treatment, and implications for disease management. *Gastroenterology*, **161** (4), 1118–1132. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8564770/.

Román, A. L. S., Muñoz, F. (2011). Comorbidity in inflammatory bowel disease. *World J. Gastroenterol.,* **17**, 2723–2733.

Ruel, J., Ruane, D., Mehandru, S., Gower-Rousseau, C., Colombel, J. F. (2014). IBD across the age spectrum: Is it the same disease? *Nat. Rev. Gastroenterol. Hepatol*., **11**, 88–98.

Schüle, S., Rossel, J. B., Frey, D.,Biedermann, L., Scharl, M., Zeitz, J., Freitras-Queiroz, N., Kuntzen, T., Greuter, T. (2017). Widely differing screening and treatment practice for osteoporosis in patients with inflammatory bowel diseases in the Swiss IBD cohort study. *Medicine*, **96**, e6788.

Slimību profilakses un kontroles centrs (2019). *Smēķēšanas izplatība un sekas Latvijā 2018. gadā*. 7. izdevums [Expansion and Consequences of Smoking in Latvia, 2018. 7th edn.]. Rīga, 2019. 14 pp. (in Latvian). https://www.spkc.gov.lv/lv/zinojumi/tematiskais-zinojums-smekesanas-izplatiba-un-sekas-latvija-2018.gada-7.-izdevums.pdf (accessed 11.01.2022).

Strober, B., Karki, C., Mason, M., Guo, N., Holmgren, S. H., Greenberg, J. D., Lebwohl, M. (2018). Characterization of disease burden, comorbidities, and treatment use in a large, US-based cohort: Results from the Corrona Psoriasis Registry. *J. Amer. Acad. Dermatol.,* **78** (2), 323–332. https://www.sciencedirect.com/science/article/pii/S0190962217325380

Su, C. G., Judge, T. A., Lichtenstein, G. R. (2002). Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol. Clin. North Amer.,* **31**, 307–327.

Sy, A., Khalidi, N., Dehghan, N., Barra, L., Carette, S., Cuthbertson, D., Hoffman, G. S., Koening, C. L., Langford, C. A., McAlear, C., Moreland, L. (2016). Vasculitis in patients with inflammatory bowel diseases: A study of 32 patients and systematic review of the literature. In: *Seminars in Arthritis and Rheumatism*, **45** (4), 475–482. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4982464/.

Turesson, C. (2016). Comorbidity in rheumatoid arthritis. *Swiss Med. Wkly,* **146**, w14290.

Vadstrup, K., Alulis, S., Borsi, A., Jørgensen, T. R., Nielsen, A., Munkholm, P., Qvist, N. (2020). Extraintestinal manifestations and other comorbidities in ulcerative colitis and Crohn Disease: A Danish Nationwide Registry Study 2003–2016. *Crohn's Colitis 360*, **2** (3), DOI: 10.1093/crocol/otaa070. https://academic.oup.com/crohnscolitis360/article/2/3/otaa070/5896668?login=true.

Van Limbergen, J., Radford-Smith, G., Satsangi, J. (2014). Advances in IBD genetics. *Nat. Rev. Gastroenterol. Hepatol.,* **11**, 372–385.

Van Onna, M., Boonen, A. (2016). The challenging interplay between rheumatoid arthritis, ageing and comorbidities. *BMC Musculoskel. Disord.,* **17**, 184.

Vavricka, S. R., Schoepfer, A., Scharl, M., Lakatos, P. L., Navarini, A., Rogler, G. (2015). Extraintestinal manifestations of inflammatory bowel disease. *Inflamm. Bowel Dis.,* **21** (8), 1982–1992. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4511685/.

Wagtmans, M. J., Verspaget, H. W., Lamers, C. B. van Hogezand, R. A. (2001). Gender-related differences in the clinical course of Crohn's disease. *Amer. J. Gastroenterol*., **96**, 1541–1546.

Yarur, A. J., Deshpande, A. R., Pechman, D. M., Tamariz, L., Abreu, M. T., Sussman, D. A. (2011). Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. *Amer. J. Gastroenterol.,* **106**, 741–747.

EKSTRAINTESTINĀLO IZPAUSMJU UN BLAKUSSLIMĪBU SLOGS ĀRSTĒTIEM UN NEĀRSTĒTIEM ČŪLAINĀ KOLĪTA UN KRONA SLIMĪBAS PACIENTIEM: LATVIJAS VALSTS MĒROGA RECEPŠU DATU BĀZES PĒTĪJUMS, 2014–2019

Iekaisīgās zarnu slimības (IZS), kas ietver Krona slimību (KS) un čūlaino kolītu (ČK) bieži pavada ekstraintestinālas izpausmes (EIM) sistēmiska autoimūna procesa dēļ, kas ir svarīgi IZS pacientu ārstēšanā un to ilgtermiņa iznākumos. Pētījuma mērķis — noteikt EIM un blakusslimību sastopamību un to slogu IZS pacientiem, pamatojoties uz Latvijas valsts mēroga kompensēto recepšu datubāzi no 2012. līdz 2019. gadam. KS un ČK pacienti no 2014. līdz 2018. gadam tika salīdzināti pēc vecuma un dzimuma ar neārstētiem IZS pacientiem un apsekoti līdz 2019. gadam. EIM tika atlasītas, pamatojoties uz iepriekš publicēto metodoloģiju un sagrupētas orgānu sistēmās. Tika pētītas atšķirības EIM/blakusslimību profilā un to attīstība laika gaitā, kā arī noteikts kumulatīvais EIM slogs. Pētījumā tika iekļauti 187 KS un 1137 ČK pacienti. Augstāka EIM prevalence tika novērota neārstētiem IZS pacientiem, savukārt ārstēto IZS pacientu grupā prevalence saglabājās skaitliski līdzīga. Ārstēto pacientu vidū visizplatītākie EIM skar sirds un asinsvadu, hepatopankreatobiliāru, endokrīno, muskuļu un skeleta, elpošanas sistēmu, kā arī ādas un zarnu trakta sistēmas, kur 28,4–79,9% IZS pacientu šo EIM pirmo reizi piedzīvoja pirms IZS diagnozes noteikšanas. Kopējam blakusslimību slogam laika gaitā bija tendence pieaugt. Pētījums sniedz pierādījumus tam, ka ārstētiem IZS pacientiem ir mazāks EIM/ blakusslimību risks, salīdzinot ar neārstētiem IZS pacientiem.