Characteristics of Patients with Crohn's Disease treated at the Inflammatory bowel disease centre of University Medical Centre Ljubljana Slovenia – updated report for 2022 from UR-CARE registry

Značilnosti bolnikov s Crohnovo boleznijo zdravljenih v Univerzitetnem kliničnem centru Ljubljana – poročilo iz UR-CARE registra za leto 2022

Zala Jagodic[1], David Drobne*[1, 2]
[1]*Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[2]*Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia*
Slovenian Journal of Digestive Diseases / Gastroenterolog 2023; 1: 6–12

***Keywords**: endoscopy, patient-reported outcomes, biomarkers, epidemiology*

***Ključne besede**: endoskopija, izhod zdravljenja, biomarkerji, epidemiologija*

ABSTRACT

Background: The epidemiology and characteristics of patients with Crohn's disease have not been reported recently in Slovenia.

Aim: To present characteristics of patients with Crohn's disease treated at the inflammatory bowel disease centre of University Medical Centre Ljubljana Slovenia.

Methods: Prospectively collected data on patient demographics and clinical, biochemical and endoscopic activity were extracted from UR-CARE Registry in October 2022.

IZVLEČEK

Izhodišče: V Sloveniji nimamo posodobljenih podatkov o epidemiologiji Crohnove bolezni in značilnostih bolezni.

Namen: Opisati značilnosti bolnikov s Crohnovo boleznijo, zdravljenih v Univerzitetnem kliničnem centru Ljubljana, Slovenija.

Metode: Prospektivno zbrane podatke o demografskih značilnostih bolnikov, klinični, biokemični in endoskopski aktivnosti bolezni smo izvozili iz UR-CARE registra oktobra 2022.

*assist. prof. David Drobne, MD, PhD
Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Slovenia
Department of Gastroenterology, University Medical Centre Ljubljana, Japljeva ulica 2, 1000 Ljubljana, Slovenia
E-mail: david.drobne@gmail.com

 Received: 3/23/2023; Review: 4/5/2023; Accepted for publication: 4/20/2023

Results: In total 947 patients (48% women) with Crohn's disease were followed in our unit. The median age was 48.7 years (interquartile range (IQR) 35.2–59.8). The median age at diagnosis was 29.0 years (IQR 20.3–42.4). The median disease duration was 13.7 years (IQR 7.7–22.7 years). Family history of inflammatory bowel disease was present in 9.3% (64/691). 146/710 (20.6%) patients were smokers, 152/710 (21.4%) were previous smokers and 412/710 (58%) never smoked. The median body mass index was 25.4 (IQR 22.7–28.5). Of most patients, 76.2% (423/555) reported no abdominal pain. However, only 55.3% (297/537) reported the absence of liquid stools. C-reactive protein was increased in 21% (49/233) and faecal calprotectin in 29% (46/156) of patients. In 52% (96/184) of patients, endoscopic remission was observed. In total 63.4% (600/947) were treated with biologicals (53.7% with TNF-alpha inhibitors, 31% with ustekinumab, and 15.3% with vedolizumab).

Conclusions: Approximately one-quarter of patients with Crohn's disease had clinically, biochemically or endoscopically active disease despite the high proportion of patients treated with biologicals.

Acknowledgements: We thank our study nurses Carmen Sekulić Bobnar, Tadeja Polanc and Andreja Planinc for help with data collection.

Rezultati: Skupno se v našem centru vodi 947 bolnikov (48 % žensk) s Crohnovo boleznijo. Mediana starosti je bila 48,7 let (interkvartilni razmak 35,2–59,8). Mediana starosti ob diagnozi je bila 29,0 let (interkvartilni razmak 20,3–42,4). Mediana trajanja bolezni je bila 13,7 let (interkvartilni razmak 7,7–22,7). Pozitivno družinsko anamnezo za kronično vnetno črevesno bolezen je imelo 9,3 % pacientov (64/691). 164/710 (20,6 %) je bilo kadilcev, 152/710 (21,4 %) je bilo bivših kadilcev in 412/710 (58 %) jih nikoli ni kadilo. Mediana indeksa telesne mase je bila 25,4 (interkvartilni razmak 22,8–28,5). Večina pacientov (76,2 % oziroma 423/555) ni imela bolečin v trebuhu, vendar pa je le 55,3 % (297/537) bolnikov ni imelo tekočih odvajanj blata. C-reaktivni protein je bil povišan pri 21 % (49/233), fekalni kalprotektin pa pri 29 % (46/156). Endoskopsko remsijo je imelo 52 % (96/184) bolnikov. Z biološkimi zdravili je bilo zdravljenih 63,4 % (600/947) bolnikov (zaviralci TNF-alfa 53,7 %, ustekinumab 31 %, vedolizumab 15,3 %).

Zaključek: Približno ena četrtina bolnikov je imela klinično, biokemično ali endoskopsko aktivno bolezen kljub velikemu deležu bolnikov na biološki terapiji.

INTRODUCTION

In the last few decades, the incidence of inflammatory bowel disease (IBD) has increased (1). For some time IBD was known as a disease of the Western world, however, more recent data suggest a rapid increase in IBD incidence in the Eastern part of the world (2). This is most likely related to industrialisation and the adoption of Westernised diet and lifestyle in the East (3).

In Slovenia, epidemiological data on IBD have not been updated since 2014. The last report by Baraga et al. indicated that the incidence of IBD in Slovenia has increased from 8.7/100.000 (from 1990 to 2000) to 18.2/100.000 (from 2001 to 2012). In this report, however, the characteristics of the disease such as disease severity, extent and medical treatment have not been reported (4).

Due to the lack of a prospective IBD registry in Slovenia, several Slovenian centres, including the clinical department for gastroenterology of University Medical Centre Ljubljana, joined the European registry – UR CARE (United Registries for Clinical Assessment and Research) in 2019. Here we report on the characteristics of patients with Crohn's disease treated at the large IBD centre of University Medical Centre Ljubljana Slovenia using the UR CARE registry data for the year 2022.

METHODS

UR-CARE Registry

In this study, we analysed the characteristics of all patients with Crohn's disease treated at the University Medical Centre Ljubljana Slovenia. UR CARE is an initiative of the European Crohn's and Colitis Organisation (ECCO) developed to facilitate daily patient care (studying disease courses, the impact of treatment on disease and outcomes of IBD) and research studies in IBD (5). In this report, we included 947 patients with Crohn's disease treated in our hospital who had at least one visit between October 2021 and October 2022. Patient data were extracted from the UR-CARE Registry on October 15th 2022.

Data extraction

We extracted the data on the demographics of the patients, such as sex, age, age at the time of diagnosis, duration of disease, weight and body mass index. Values were expressed as medians with an interquartile range. We also analysed the data on disease extension, disease activity and pharmacologic therapy. Disease extension was reported as the maximum disease extension. Disease extension was assessed from all available clinical data such as endoscopy, histology, cross-sectional imaging, and surgical reports.

Clinical and biochemical disease activity

To assess clinical disease activity, we used 3 components of the Harvey-Bradshaw index (general well-being, abdominal pain and number of liquid stools per day) as those are collected prospectively through the UR-CARE interface in our centre. We used the last available (most recent) value reported in the Registry.

To assess biochemical disease activity, we extracted data on biomarkers (C-reactive protein and faecal calprotectin) that were available in the Registry. Faecal calprotectin was measured with the Calprest assay with a range from 15.6 to 500 mg/kg (Eurospital, Trieste, Italy). To avoid false negative results, patients were advised to collect the first-morning stool sample and to deliver it to the laboratory within 24 hours. C-reactive protein was measured with the ADVIA 1800 Chemistry System (Siemens, Germany).

Endoscopy

Patients in our hospital have endoscopies performed for establishing the diagnosis and to assess response to treatment (6). For this report, endoscopic data were collected retrospectively. For most of our endoscopy's composite (not per segment) Simple Endoscopic Score for Crohn's Disease (SES-CD) was reported. Therefore, only the total SES-CD is reported in this report. SES-CD is nowadays routinely used to determine the endoscopic activity of Crohn's disease. It assesses the presence and size of ulcers, the extent of ulcerated surface, the extent of affected surface and the presence of narrowing in 5 segments of the digestive tract (rectum, left colon, transverse colon, right colon, ileum). Endoscopic activity is scored by composite points of all segments (higher number meaning higher disease activity: 0 to 2 points reflects endoscopic remission, 3–6 points for mild endoscopic activity, 7–15 points for moderate endoscopic activity and more than 15 points for severe endoscopic activity) (7) (8). The assessment of the SES-CD score is summarised in Figure 1.

	SES-CD values			
Variable	0	1	2	3
Ulcers	None	Aphthous ulcers (Diameter 0.1-0.5 cm)	Large ulcers (Diameter 0.5-2 cm)	Very large ulcers (Diameter >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Figure 1

RESULTS

General demographic characteristics

Out of 1899 patients with Inflammatory bowel disease followed in our centre at the time of data extraction, 947 (49.9%) were diagnosed with Crohn's disease. Of these, 456/947 (48.2%) were women and 491 (51.8%) were men. The median patient's age was 48.7 years (interquartile range (IQR) 35.2–59.8), while the median age at diagnosis of Crohn's disease was 29.0 years (IQR 20.3–42.4). The median disease duration was 13.7 years (IQR 7.7–22.7 years). Family history of inflammatory bowel disease was reported in 9.3% of patients (data available for 691 patients). Smoking data were available for 710 patients: 146/710 (20.6%) were smokers, 152/710 (21.4%) were previous smokers and 412/710 (58%) never smoked. Information about Body mass index (BMI) data were available for 303 patients. Median BMI was 25.4 (IQR 22.7–28.5).

Maximum disease extension is shown in Figure 2.

Clinical disease activity

Data on clinical disease activity are summarized in Figure 3 (general well-being, data available for 556 patients), Figure 4 (abdominal pain, data available for 555 patients) and Figure 5 (number of liquid stools per day, data available for 537 patients).

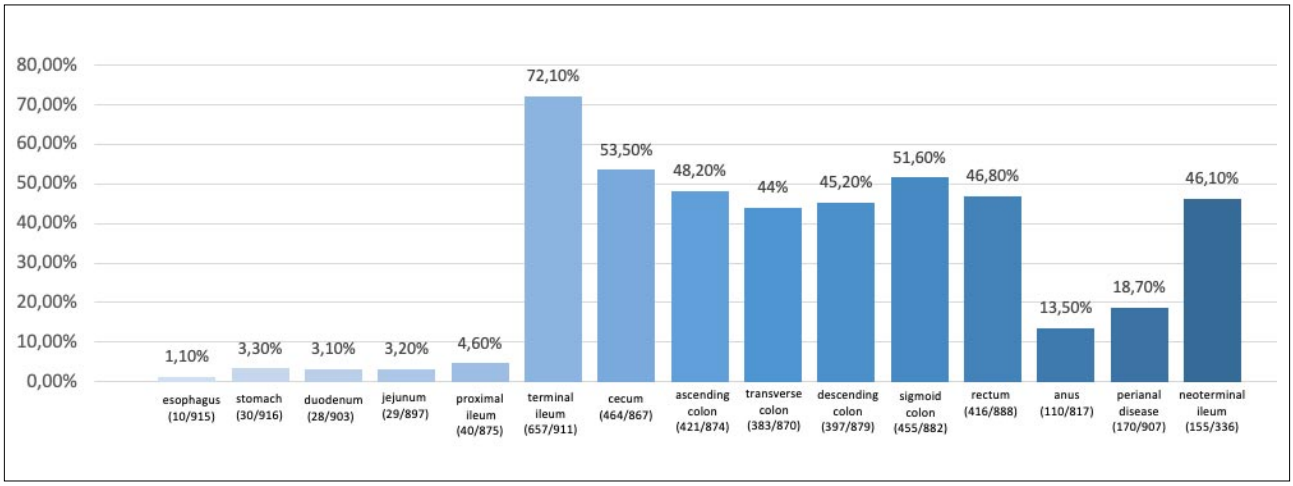

Figure 2

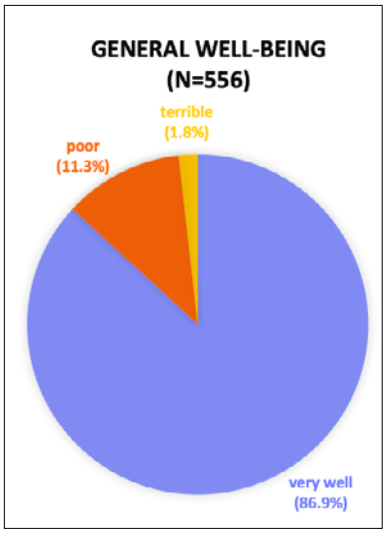

Figure 3

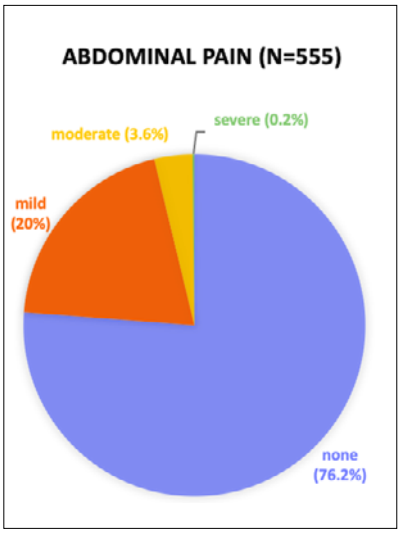

Figure 4

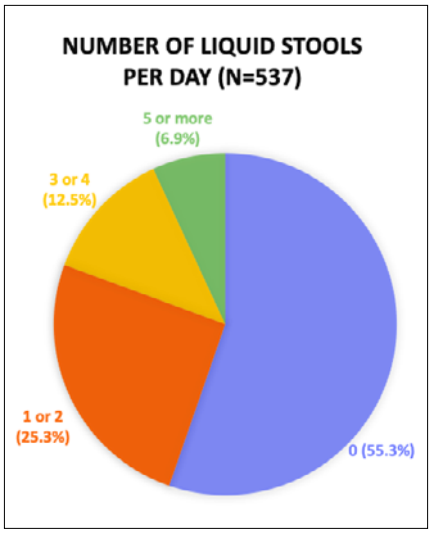

Figure 5

Biochemical disease activity

Faecal calprotectin and C-reactive data were available for 156/947 (16.5%) and 233/947 (24.6%) patients, respectively. Results are summarised in Figures 6 and 7.

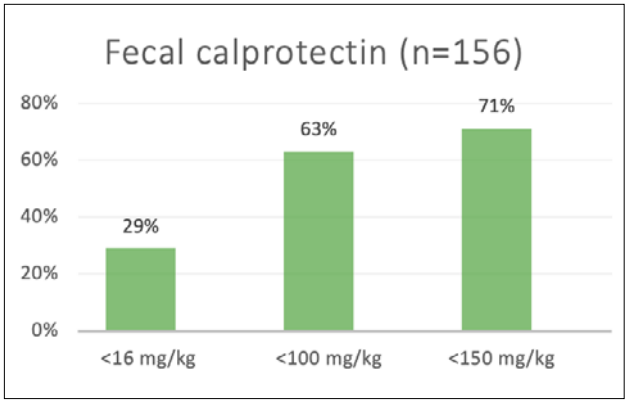

Figure 6

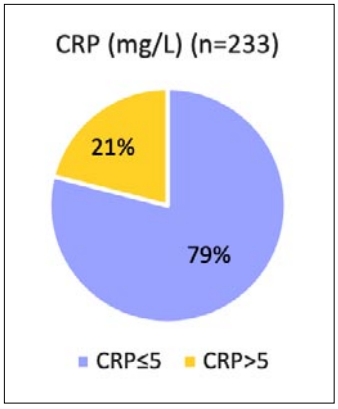

Figure 7

Endoscopic disease activity

Endoscopic data were available for 184/947 (19%) of patients. Endoscopic activity as assessed by SES-CD score is shown in Figure 8.

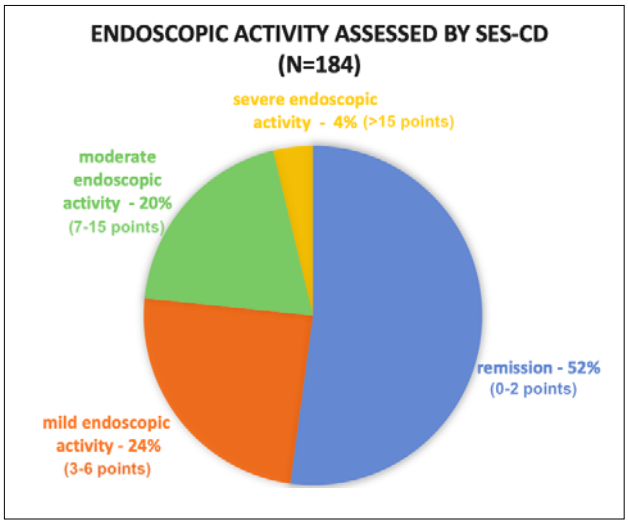

Figure 8

Biological therapy

At the time of data extraction, 600/947 (63,4%) patients with Crohn's disease were treated with biological treatment. The distribution of different biological drug classes is shown in Figure 9.

DISCUSSION

In this study, we report on the large single-centre cohort of patients with Crohn's disease treated at the tertiary referral centre. Around two-thirds of patients had small bowel disease, and one in five patients suffered from perianal involvement. Therefore, it is not surprising that 63% of this refractory cohort were treated with biologicals. Still, as many as 20% of patients had clinically, biochemically or endoscopically active disease.

As expected, the most commonly affected segment was the terminal ileum (affected in 72.1% of patients), which is in line with other reported cohorts. A national study in Colombia found that 37.7% of Crohn's disease patients had the ileocolonic disease and 37.1% had isolated terminal ileum disease (9). Epidemiological data from Malaysia shows that 22.7% of patients with Crohn's disease had isolated ileal disease and 47.7% ileocolonic disease (10). Similarly, our 18.7% rate of perianal fistulizing disease is in line with other reports (11, 12). For example, 19% of Danish

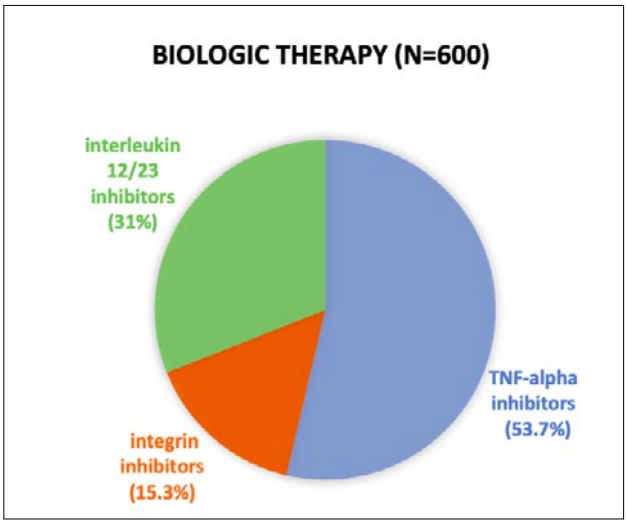

Figure 9

nationwide cohort study patients developed perianal disease (13).

In 46% of cases, new terminal ileum was affected in our cohort. Since many patients in our centre as per local clinical practice received postoperative prophylactic treatment with TNF-alfa inhibitor we might have underestimated postoperative Crohn's disease recurrence. This is reflected in higher recurrence rates reported in cohorts without such an approach, where as many as 36% to 86% have endoscopic evidence of disease activity in the new terminal ileum by 10 years of surgery (14–16).

The great majority of patients in our cohort had good control of clinical symptoms as evidenced by no or mild abdominal pain. Although this is of paramount importance for a patient's quality of life it is still important to achieving biochemical remission and endoscopic remission to prevent delayed complications. Therefore, an increased CRP of 21% and faecal calprotectin of 29% stress that many of our patients still did not have complete disease control. Since these two biomarkers are determined at routine visits, we believe that this estimation of disease burden is correct. This is even more worrisome since it has been reported that as many as 15% of patients fail to generate a CRP response to active inflammation in the bowel (17). By setting more stringent criteria (i. e. decreasing faecal calprotectin cut-off values) for biochemical remission even more patients failed to achieve biochemical disease remission.

Our results show that 52% of patients had no endoscopic activity as assessed by the SES-CD score, meaning they were in endoscopic remission at the time of performing the endoscopy. However, it is important to mention that endoscopies were indicated for different reasons (e. g. dysplasia surveillance). Also, data were available only for 184/947 (19%) of patients. For these reasons, our endoscopic data should be interpreted carefully. Because of these limitations, we believe that our endoscopic data are an overestimation of disease control in our cohort.

The proportion of patients treated with biologicals in our cohort was high compared to Eastern Europe (18) but in line with West Europe and the USA (19, 20). Inhibitors of TNF-alpha were used in the majority of patients. We, however, did not have data on changing trends for the prescription of novel biologicals in our cohort, such as vedolizumab or ustekinumab. Also, we did not have data on disease duration at the start of biologicals (21). Also, therapeutic drug monitoring, with the potential for improving outcomes, has only recently been fully incorporated into clinical practice in our hospital (22). Because of these limitations, we were not able to assess whether low rates of disease control could be explained by delayed initiation of biologicals.

In conclusion, despite high access to biologicals in Slovenia, still up to one-quarter of patients had clinically, biochemically and endoscopically active disease. This underlines the need for future drug development for patients with Crohn's disease.

References

1. Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet* 2017; 390:2769-78. doi:10.1016/S0140-6736(17)32448-0.
2. Mak WY, Zhao M, Ng SC, *et al.* The epidemiology of inflammatory bowel disease: East meets west. *J Gastroenterol Hepatol* 2020; 35:380-9. doi:10.1111/jgh.14872.
3. Zhao M, Gönczi L, Lakatos PL, *et al.* The Burden of Inflammatory Bowel Disease in Europe in 2020. *J Crohns Colitis* 2021; 15:1573-87. doi:10.1093/ecco-jcc/jjab029.
4. Dušan Baraga IF. Epidemiologija bolnikov s kronično vnetno črevesno boleznijo v družinski medicini. *Gastroenterolog* 2014; :10-7.
5. Burisch J, Gisbert JP, Siegmund B, *et al.* Validation of the 'United Registries for Clinical Assessment and Research' [UR-CARE], a European Online Registry for Clinical Care and Research in Inflammatory Bowel Disease. *J Crohns Colitis* 2018; 12:532-7. doi:10.1093/ecco-jcc/jjy015.
6. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; 110:1324-38. doi:10.1038/ajg.2015.233.
7. Daperno M, D'Haens G, Van Assche G, *et al.* Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; 60:505-12. doi:10.1016/s0016-5107(04)01878-4.
8. Van Assche G. Moskovitz DN, Daperno M. Defining and validating cut-offs for the Simple Endoscopic Score for Crohn's Disease. *Gastroenterol* 2007.
9. Juliao-Baños F, Kock J, Arrubla M, *et al.* Trends in the epidemiology of inflammatory bowel disease in Colombia by demographics and region using a nationally representative claims database and characterization of inflammatory bowel disease phenotype in a case series of Colombian patients. *Medicine (Baltimore)* 2021; 100: e24729. doi:10.1097/MD.0000000000024729.

10. Mokhtar NM, Nawawi KNM, Verasingam J, *et al.* A four-decade analysis of the incidence trends, sociodemographic and clinical characteristics of inflammatory bowel disease patients at the single tertiary centre, Kuala Lumpur, Malaysia. *BMC Public Health* 2019; 19:550. doi:10.1186/s12889-019-6858-2.
11. ENiGMA CODE collaborators. Development of a core descriptor set for Crohn's anal fistula. *Colorectal Dis Off J Assoc Coloproctology G B Irel* Published Online First: 3 December 2022. doi:10.1111/codi.16440.
12. Gecse KB, Bemelman W, Kamm MA, *et al.* A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014; 63:1381-92. doi:10.1136/gutjnl-2013-306709.
13. Wewer MD, Zhao M, Nordholm-Carstensen A, *et al.* The Incidence and Disease Course of Perianal Crohn's Disease: A Danish Nationwide Cohort Study, 1997-2015. *J Crohns Colitis* 2021; 15:5-13. doi:10.1093/ecco-jcc/jjaa118.
14. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. *Br J Surg* 2000; 87:1697-701. doi:10.1046/j.1365-2168.2000.01589.x.
15. Hanzel J, Drobne D. Contemporary Management of Postoperative Crohn's Disease after Ileocolonic Resection. *J Clin Med* 2022; 11:6746. doi:10.3390/jcm11226746
16. Olaison G, Smedh K, Sjödahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. *Gut* 1992; 33:331-5. doi:10.1136/gut.33.3.331.
17. Mosli MH, Zou G, Garg SK, *et al.* C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015; 110:802-19. doi:10.1038/ajg.2015.120.
18. Kucha P, Zagórowicz E, Walkiewicz D, *et al.* Biologic treatment of inflammatory bowel disease in Poland, 2012-2020: nationwide data. *Pol Arch Intern Med* 2022; 132:16287. doi:10.20452/pamw.16287.
19. Bähler C, Vavricka SR, Schoepfer AM, *et al.* Trends in prevalence, mortality, health care utilization and health care costs of Swiss IBD patients: a claims data based study of the years 2010, 2012 and 2014. *BMC Gastroenterol* 2017; 17:138. doi:10.1186/s12876-017-0681-y.
20. Alulis S, Vadstrup K, Borsi A, *et al.* Treatment patterns for biologics in ulcerative colitis and Crohn's disease: a Danish Nationwide Register Study from 2003 to 2015. *Scand J Gastroenterol* 2020; 55:265-71. doi:10.1080/00365521.2020.1726445.
21. Drobne D. UR-CARE - evropski register bolnikov s kronično vnetno črevesno boleznijo: izkušnje po prvih 1000 vključenih bolnikov na Kliničnem oddelku za gastroenterologijo v Ljubljani = UR-CARE - European Inflammatory Bowel Disease Registry. *Gastroenterolog* 2021; 25:5-13.
22. Papamichael K, Afif W, Drobne D, *et al.* Therapeutic drug monitoring of biologics in inflammatory bowel disease: unmet needs and future perspectives. *Lancet Gastroenterol Hepatol* 2022; 7:171-85. doi:10.1016/S2468-1253(21)00223-5.