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North-Western register of patients with inflammatory bowel disease: achievements and lessons learned

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ABSTRACT The problem of inflammatory bowel disease (IBD) — ulcerative colitis (UC) and Crohn's disease (CD) has not lost its urgency for several decades. Patients with IBD require long-term, continuous, often lifelong therapy and follow-up. This paper presents the data of patients' register, worked out in Mechnikov North-Western State Medical University, in the Centre of IBD treatment.

As per the Register, an average time of diagnosis was 2.6 years (30.7 months) — for CD and 1.1 year (12.7 months) — for UC. At the same time, only 36.9% of CD patients versus 72% of UC patients were diagnosed within the first year, with the peak incidence at the age between 18 and 30 years.

Extra-intestinal manifestations are marked in 43.5% of CD patients and in 23.2% of UC patients. Besides, a quarter of them have more than one extra-intestinal symptoms, with bone and joint involvement domination (in 29.2% of CD patients and 18.4% of UC patients).

Epidemiological registers, including IBD registers, form an important database on the incidence, characteristics, regional distribution, and nature of the disease development, which helps to navigate the profile of patients, investigate possible causes and determine risk factors affecting its course.

However, the unified Federal Register will allow us to get a complete picture of patients with IBD in the country. In addition, maintaining a national register and pharmaco-economical evaluation of various treatment methods will, in our opinion, optimize treatment costs; ensure rational planning and use of budgetary funds.

KEYWORDS: inflammatory bowel disease, Crohn's disease, ulcerative colitis, registry, epidemiology

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INTRODUCTION

The problem of inflammatory bowel diseases (IBD) — ulcerative colitis (UC) and Crohn's disease (CD) has not lost its relevance for several decades.

This is a consequence of the absence of an established etiological factor, the need for multidisciplinary diagnostic and treatment approaches. Nevertheless, patients with IBD are a category of patients who need long-term, continuous, often lifelong treatment and supervision. Recently, the strategy of IBD therapy is aimed at achieving deep remission, implying not only clinical and endoscopic remission, but also a decrease in the severity of histological inflammation.

Given the immuno-mediated nature of the pathology, IBD treatment regimens often include the use of immunosuppressive and genetically engineered biological therapy (GEBT), which has pathogenetic application points from the basis of evidence-based medicine.

An important fact is that the selection of medications for patient with IBD should be carried out individually, including taking into account the tolerability, effectiveness and assessment of the likelihood of undesirable effects of the therapy.

There is no generalized information on the prevalence and incidence of IBD in the Russia. However, indirectly, the increase in the IBD incidence is evidenced by the steady increase in the number of hospitalizations for UC and CD.

Thus, for the period between 2011 and 2017, the number of hospitalized patients with ulcerative colitis almost doubled — from 10,326 to 19,656 cases, the rate of hospitalizations for emergency indications as well as the level of hospital mortality remained almost unchanged [1–3].

According to publications of international authors, the prevalence and incidence of IBD is growing. Thus, the prevalence of inflammatory bowel diseases exceeded 0.3% in North America, Oceania, and in many European countries. Since 1990, the increase in morbidity according to the literature is from 4% to 11.1% for CD and from 4.8% to 14.9% for UC [4]. According to the conducted meta-analyses and reports, it can now be said that the greatest prevalence of IBD is in Europe (UC: 505 /100 thousand — in Norway; CD: 322 /100 thousand — in Germany) and North America (UC: 286 / 100 thousand — in the USA; CD: 319 /100 thousand — in Canada) [4].

An Israeli study of the population prevalence of IBD, published in 2019, demonstrated a significant increase in morbidity (by 6 and 8 times, for CD and UC, respectively), as well as a decrease in the age of onset of clinical manifestations. These studies demonstrate an increase in the annual prevalence of UC from 16 to 128 cases, and CD from 42 to 425 cases per 100 thousand people. At the same time, the average age of onset of the disease decreased from 15.0 ± 2.8 years in 2002–2008 to 14.3 ± 3.1 years in 2009–2016 ($p < 0.0001$) [5]. A thirty-year longitudinal population study of IBD in Korea for the period between 1985 and 2015 also demonstrated an increase in morbidity over the past three decades.

Thus, the average annual incidence of CD and UC per 100,000 people increased from 0.06 (95% CI 0.05–0.07) and 0.29 (95% CI 0.27–0.31), respectively, registered in the period between 1986 and 1990, to 2.44 (95% CI 2.38–2.50) and 5.82 (95% CI, 5.73–5.92), respectively, in the period between 2011 and 2015. The average annual percentage change in the incidence of IBD was 12.3% in 1986–1995, 12.3% in 1996–2005 and 3.3% in 2006–2015 [6].

IBD can be diagnosed at any age. However, the most common age of onset of symptoms is young age. Patients with CD have higher risks of

premature death compared to the general population; and in general, the cohort of people with IBD has higher risks of developing colorectal cancer [1,7–10].

In general, according to the results of studies in recent years, about 25% of patients with UC need emergency or urgent care during the entire period of their disease. For the 5-year follow-up period in the Epi-IBD study, it was noted that 6% of patients underwent colectomy, and the incidence of hospitalizations was 23% [1,11,12]. Of course, mortality rates have significantly decreased if we analyze the reports available in the time interval. Thus, at the beginning of the twentieth century, mortality in UC reached 75% in the first year from the onset of the disease, with a decrease to 17–20% by the third or more year of the duration of the patient's illness (Hardy, T.L., Bulmer, E., Br Med J. 1933) [13]. But the need for surgical treatment of patients with IBD remains at a high level, often emphasizing the ineffectiveness of drug treatment and the incidence of complicated forms, including lightning colitis, perforation, strictures, bleeding, the development of dysplasia, or malignant neoplasms, and other complications [14].

Taking into account the facts of the absolute urgency of the IBD problem, the need to assess the dynamics of morbidity, the incidence of hospitalizations, surgeries, understanding the structure of the patients cohort, the needs for a particular therapy, as well as the importance of monitoring the response to therapy aimed at reducing the risks of IBD complications, the creation of a single database, in other words, a clinical register of patients, becomes an urgent issue.

Epidemiological registers form the most important database on the incidence, regional distribution, and temporary development of certain diseases among the population.

This characterizes the prevalence, incidence or spread and course of diseases, investigates possible causes of the disease and determines risk factors affecting the disease, as well as regional differences and changes over time [15].

In addition, registers allow to monitor and evaluate the effectiveness and safety of therapeutic care for patients. The register data can serve

as a basis for clinical research: in addition to generating hypotheses and planning the number of cases (sampling bases) [16].

It is also possible to monitor the safety and effectiveness of therapy in groups of patients who usually do not participate in clinical trials (pregnant women, children, the elderly, patients with mild disease activity, comorbid patients, and other groups).

An important feature of registers, in contrast to clinical trials, limited by a clear time frame, is the observation time. A striking example is Sweden's over 50-year experience in creating the National Patient Registry since 1964, combining blocks on various diseases, hospitalizations, and operations, which are interconnected and complementary [17].

The 2015 EpiCom study on the evaluation of patient registers and registries in Europe (38 countries) showed that IBD registries were created in 19 countries, and in 15 countries there is a biobank with bio-samples. Despite the heterogeneity of the information entered between countries, such registers are an invaluable source of information for future studies of IBD [18].

In Russia, there is no single register of patients with IBD, including the clinical characteristics of the disease; and most importantly, there is no standard approach to collecting statistical information today. In this regard, it is relevant to analyze the conditions for the creation of standardized registers in order to create a national register and introduce it into practical healthcare in various regions of the Russian Federation.

Epidemiology of IBD According to the North-Western Register: General Characteristics

To date, there are only mosaic regional registers of patients with IBD in our country, which often have different evaluation criteria. It is necessary to create regional registers that would be filled in according to one sample, as fragments of the Federal Register of Patients with IBD. In 2015, the first participants in the Federal Register were the State Research Center of Coloproctology of the Health Ministry of Russia and Moscow Clinical Research and Practical Center of the Moscow Health Department.

Since February 2017, the North-Western IBD Treatment Center of the MNWSMU has also begun implementing this dynamic task. The search for participants is carried out in various ways: retrospectively, by actively inviting a patient to visit, or during the current hospitalization in the MNWSMU clinic.

Data entry is carried out with the voluntary written consent of patients, who are informed that their personal data is entered in the general electronic registration system. Patients have the right to refuse this. A form fulfilled for each patient supplements the primary documentation. The introduction of patients into the Registry does not affect the treatment and diagnostic approach carried out at this moment at the outpatient or inpatient stages.

As of 01.12.2021, the data of 1,379 patients with an established diagnosis of IBD were entered and analyzed in the Register of the Northwestern IBD Treatment Center of the MNWSMU (hereinafter — the Northwestern IBD Register), of whom 568 (41.2%) were diagnosed with CD and 811 (58.8%) were diagnosed with UC, i.e., the ratio of UC and CD is 1.43 (Fig.1).

According to the literature, in developed countries this ratio is close to 1, whereas in Asian countries the share of UC exceeds CD by 2 or more times [19,33]. The majority (96%) were patients living in St. Petersburg, which makes it possible to regard the register data as locally specific. The age of patients in the Register ranged from 20 to 76 years for UC, from 16 to 74 years for CD. Analysis of the data available in the Register shows that the peak of the onset of symptoms of both UC and CD occurs in young patients aged between 18 and 30 years (Fig.2).

According to the Register, in patients with UC, the duration of symptoms before diagnosis was no more than 2 years in 89.3% of cases. However, in 6.2% of patients, this interval was 3–5 years, in 3.2% — 6–10 years, in 1.3% — over 10 years (Fig.3). Among patients with CD, 72.6% were diagnosed within 2 years from the onset of clinical symptoms, in 14.3% — after 3–5 years, in 16.7% — 3–5 years, in 16.4% — 6–10 years, in 6.7% — after more than 10 years (Fig.3).

In patients with CD, only 36.9% of cases were diagnosed during the first year (in patients with

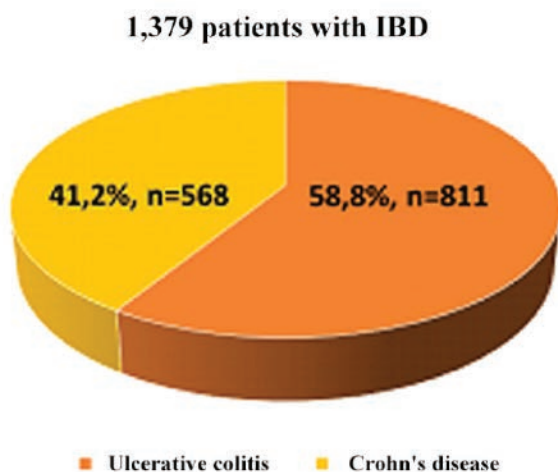


Figure 1. Nosological structure

UC — in 72% of cases), which is probably due to diagnostic difficulties, as well as late getting treatment, including in specialized centers.

The mean time from the onset of symptoms to diagnosis establishment is currently, according to the IBD Registry, 2.6 years (30.7 months) for CD, 1.1 years (12.7 months) for UC (Fig.4).

According to the literature data and the results of reports of large centers, in general, in Russia the average time of diagnosis from the moment of the first symptoms of the disease is from 1

to 1.5 years — with UC and 2.5–3.5 years — with CD. Late, untimely diagnosis leads to an increase in the number of severe forms of the disease [20–23,34].

Severity and Variants of the Course of IBD

Currently, there is a change in the course of IBD towards greater variability of symptoms, inconsistency of clinical symptoms with the actual severity of inflammation, an increase in the proportion of patients with extra-intestinal manifestations and resistance to induction and basic therapy agents.

According to the Register, left-sided lesion prevails among patients with UC — 52.5% of patients, total colitis (34.4%) is in second place in incidence, and proctitis (with an incidence of 13.1%) is in third place (Fig.5).

The number of UC recurrences in patients of the observed cohort over the past 12 months in 87% was limited to the range of 0–1, that is, the current activity at the time of entry into the database. In 6% of patients, recurrent attacks were noted during the first year of follow-up, in 7% of patients there were more than three attacks for 12 months, that is, continuous activity of the disease was recorded (Fig.6).

The dominant UC activity incidence was mild and moderate — in 35.2% and 38.8%, respectively,

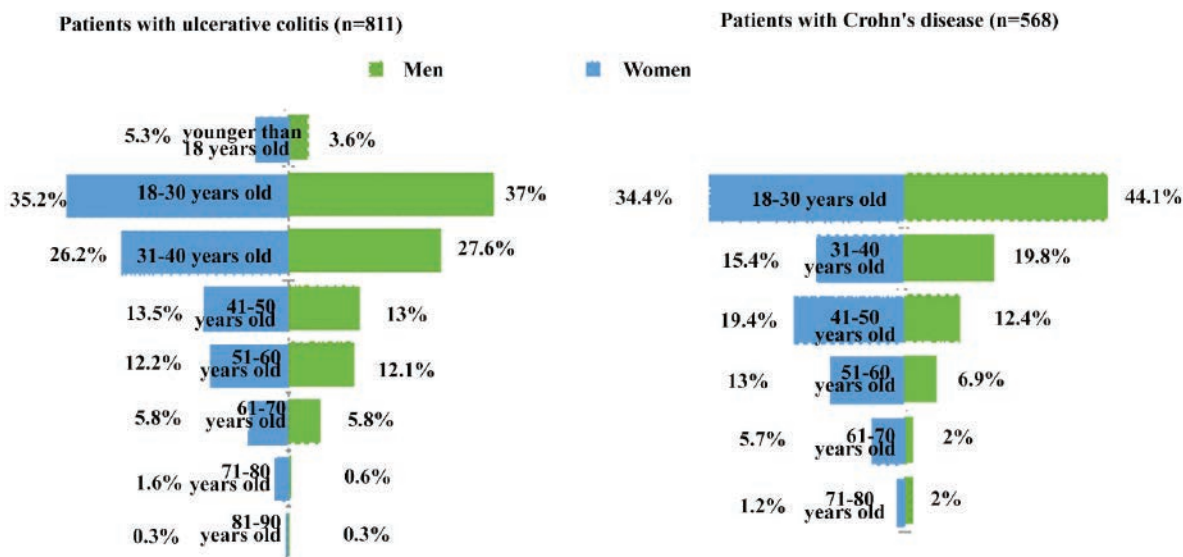


Figure 2. Distribution of patients with ulcerative colitis and Crohn's disease by sex and age groups of the onset of the first symptoms of the disease

in 0.8% of patients the episodes of exacerbation were severe, in 0.5% of patients ($n = 10$) acute severe UC attack was recorded (Fig.6).

If we take into account not only the activity of the current attack, but also history of the disease, response to therapy, presence of complications, and extra-intestinal manifestations, then

the severity of the UC overall is manifested as follows: mild attack is noted in 51.3% of patients included in the Register, moderate and severe ones are noted in 43.6% and 5%, respectively (Fig.7). According to existing approaches, the use of a particular severity assessment system in IBD is determined by the routine practice of a particular medical institution [9, 10]. In our opinion, both in the management of registers and in the management of patients in clinical practice, it is extremely important to take into account the "general" severity of the course in UC and CD. For example, when a patient showing remission or mild activity is initially entered into the register (despite having a history of severe attacks and/or surgical

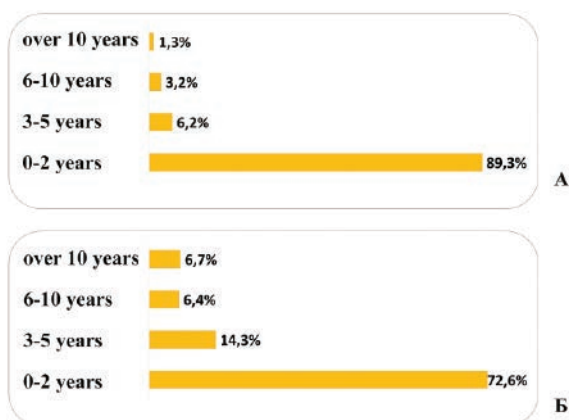


Figure 3. Timing of initial diagnosis for patients with ulcerative colitis (A) and Crohn's disease (B)

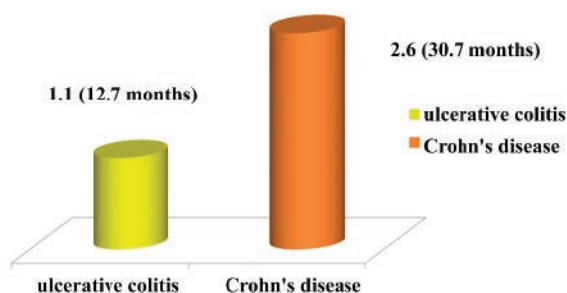


Figure 4. Average duration from symptom onset to diagnosis of IBD

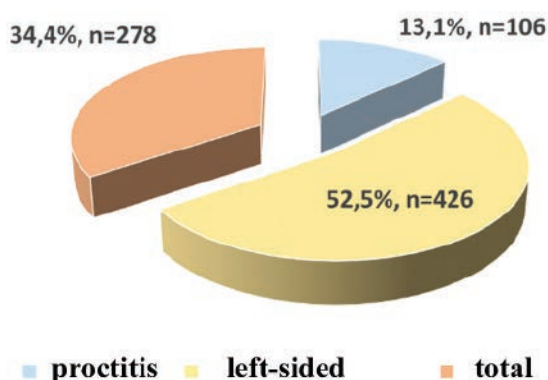


Figure 5. The structure of patients in the Northwestern IBD register as of 01.12.2021 according to the localization of ulcerative colitis ($n = 811$)

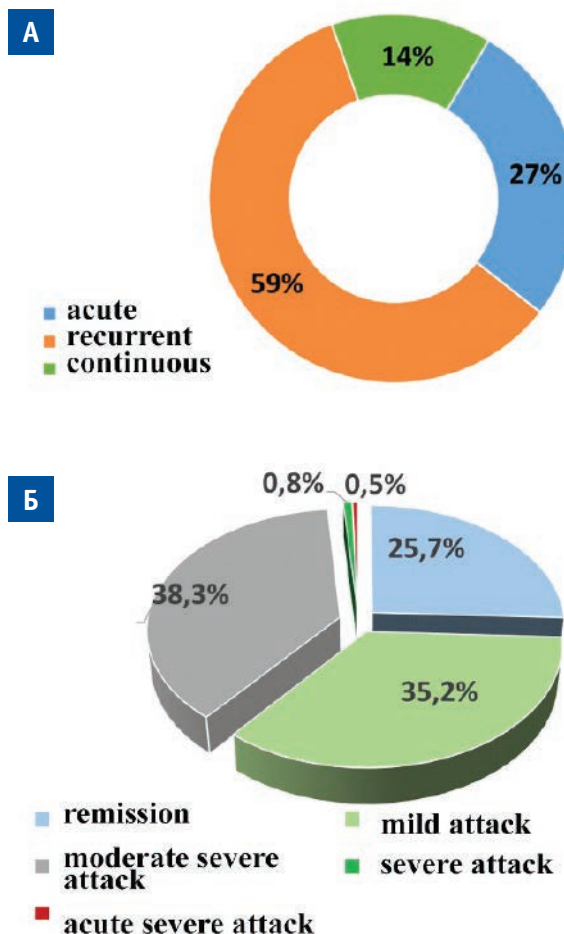


Figure 6. The structure of patients in the Northwestern IBD register as of 01.12.2021 by: A) the nature of the course; B) activity of ulcerative colitis ($n = 811$) (data from the last visit to the IBD center)

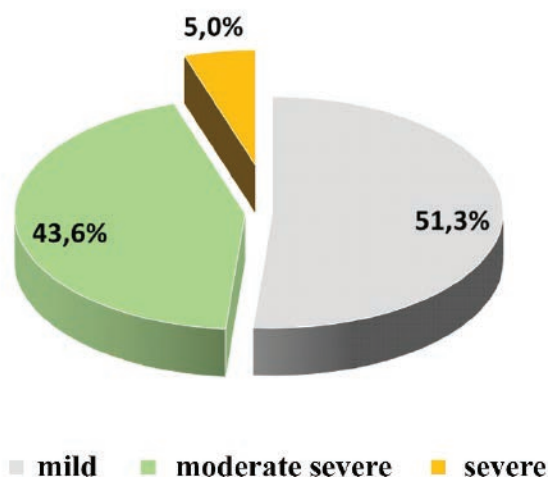


Figure 7. Distribution of patients in the Register with ulcerative colitis by the severity of the disease, $n = 811$ (data from the North-Western IBD register as of 01.12.2021)

procedures due to the course of IBD), in some cases it allows specialists to assess the severity of the course of the disease in such a patient as mild. Underestimating all the disease history in this case can lead to incorrect approach. Equally, taking into account the “general” severity of the course when maintaining registers will avoid distortion in the assessment of the analyzed group of patients on the scale of the whole region and country.

When assessing the severity of ulcerative colitis, we used the following criteria:

- 1) Mild disease: the activity of the attack always corresponds to the minimal, moderate

activity of the first attack is acceptable; a good response to 5-ASA therapy (including the first attack); the patient has no extra-intestinal manifestations; there have been no operations for UC; the recurrence rate is not over 1 time a year;

- 2) Moderate severe disease: the predominant activity of attacks in the anamnesis is moderate, including those requiring steroids therapy; and/or the patient may have extra-intestinal manifestations depending on the activity of IBD; no operations for UC; and/or steroid dependence; the recurrence rate is not over 2 times a year; it is possible to control the activity of UC conservatively;
- 3) Severe disease: the activity of attacks in the history is from moderate to fulminant; and/or the patient has extra-intestinal manifestations unrelated to the activity of IBD and leading to a significant violation of organ function (PSC, SpA, etc.); and/or the recurrence rate is 3 or more times a year; and/or steroid resistance; and/or surgery for UC was performed; and/or the activity of conservative treatment cannot be controlled.

Among the patients with CD included in the IBD Register, the most common category by location is ileocolitis (in 40.8% of cases), followed by colitis (26.8%) and terminal ileitis (32.4%) (Fig.8). Perianal lesion in the cohort was noted in 14.75% of cases. Among the forms of CD, according to the register, the most common non-stenosis/non-penetrating (inflammatory-infiltrative) form of the disease was found in 69.8% of cases, penetrating was detected in 7.5%, stenosis in 21.5%, and mixed in 1.2%.

Among patients with CD at the time of the IBD register database slice, 25.4% of patients were in remission of the disease, 31% of patients had mild activity (as per the Best index: 150–220 points), 35.4% of patients had moderate activity (as per the Best index: 220–450 points), and 8.2% — severe activity (as per the Best index: over 450 points) (Fig.9). The distribution according to the severity of the disease is as follows: 32% — mild CD, 42.7% — moderate severe, and 25.3% — severe (Fig.9).

When assessing the severity of Crohn’s disease, we used the following criteria:

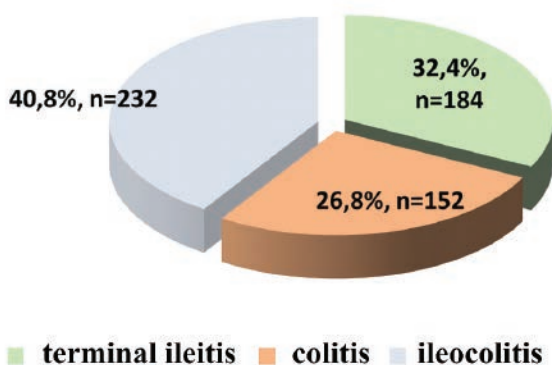


Figure 8. The structure of patients in the North-Western IBD register by localization of Crohn’s disease as of 01.12.2021 ($n = 568$)

- 1) Mild disease: the activity of the attack always corresponds to the minimal, moderate activity of the first attack is acceptable; a good response to initial therapy with remission; the patient has no extra-intestinal manifestations; there are no perianal manifestations; there are no external functioning fistulas; no urgent operations for CD was and is required; the recurrence rate is not over 1 time a year;
- 2) Moderate severe disease: the predominant activity of attacks in the history is moderate, including those requiring therapy with repeated courses of steroids; and/or the patient may have extra-intestinal manifestations depending on the activity of IBD; and/or the presence of perianal CD; and/or the presence of a functioning external

intestinal fistula; no urgent operations was and is required for CD; the recurrence rate is not over 2 times a year; and/or steroid dependence was detected; and it is possible to control the IBD activity with conservative treatment;

- 3) Severe disease: in the history there are attacks of moderate to severe activity; and/or the patient has extra-intestinal manifestations unrelated to IBD activity and leading to significant organ dysfunction (PSC, SpA,

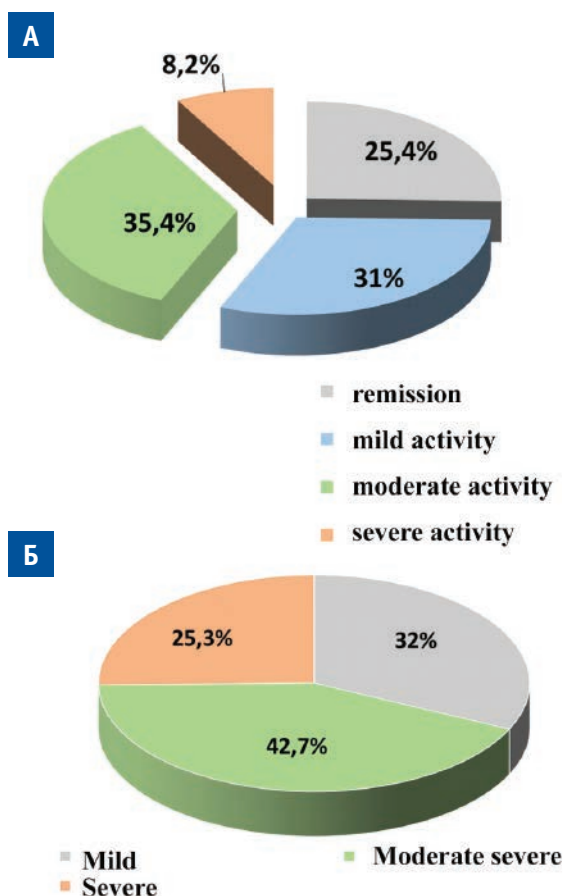


Figure 9. The structure of patients in the North-Western IBD register as of 01.12.2021 by: A) Crohn's disease activity (data from the last visit to the IBD center, $n = 568$); and Б) the severity of Crohn's disease at the time of the report, $n = 568$)

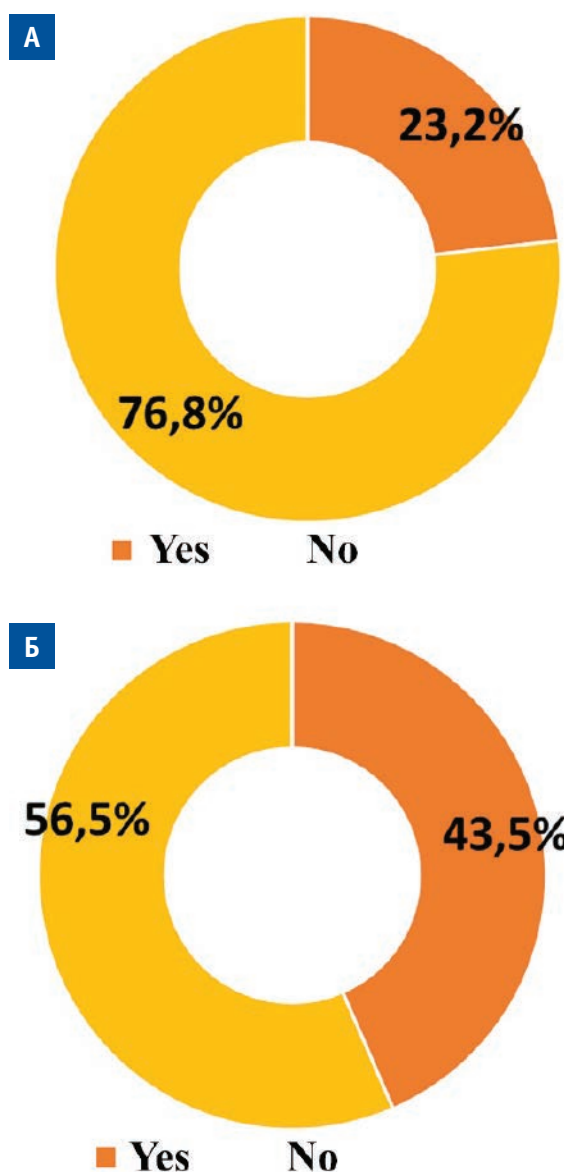


Figure 10. Distribution according to the presence of extra-intestinal manifestations A) in patients with Crohn's disease; Б) in patients with ulcerative colitis

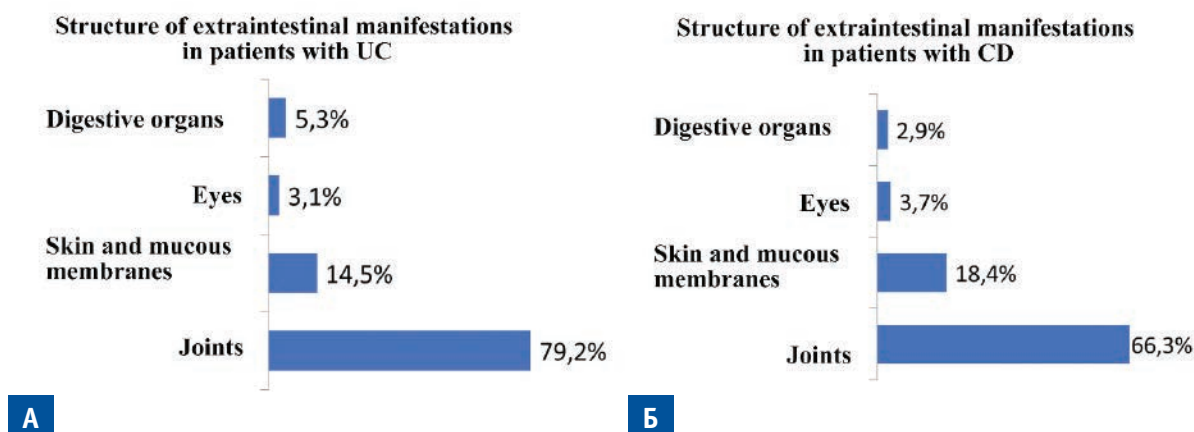


Figure 11. The structure of the identified extraintestinal manifestations A) in patients with ulcerative colitis; B) in patients with Crohn's disease

etc.); and/or severe perianal manifestations requiring surgery; and/or recurrence rate is 3 or more times a year; and/or surgery for CD have been performed; and/or currently there are complications of CD requiring surgery; and/or activity of conservative treatment cannot be controlled.

Intestinal complications among patients with CD were noted in 41.5%. Their structure included abdominal mass (16.6%), fistulas (13.1%),

abdominal abscesses (4.9%), intestinal strictures (50.8%).

Extraintestinal Manifestations

IBD is often associated with the extra-intestinal manifestations, some of which are significantly relieved or cured by treatment, while others do not depend on the underlying inflammatory process.

The incidence of extraintestinal symptoms in patients with IBD, according to the literature, can reach 50–60% [24–26]. The assessment of

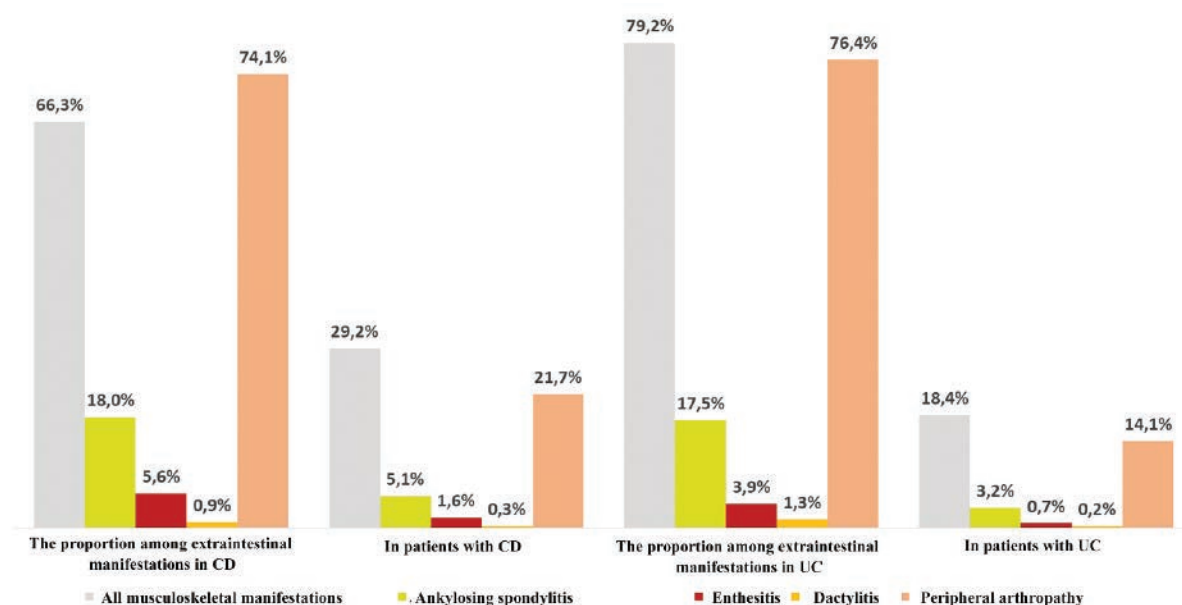


Figure 12. The structure of the identified articular extraintestinal manifestations in patients with ulcerative colitis and Crohn's disease

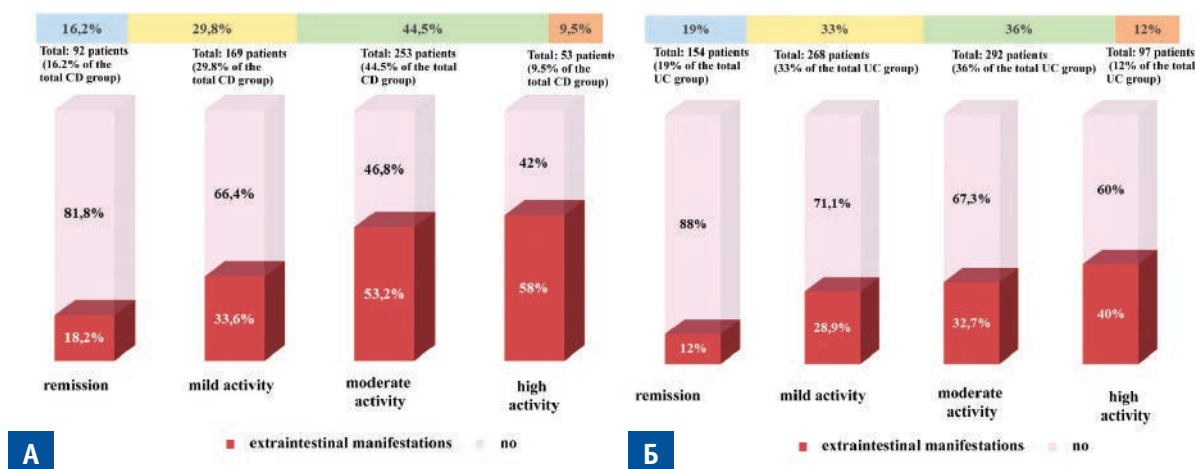


Figure 13. The frequency of detection of extraintestinal manifestations depending on the activity of the inflammatory process: A) in patients with Crohn's disease; B) in patients with ulcerative colitis

the actual prevalence is complicated by the fact that one patient may have more than one extraintestinal manifestations. Thus, the results of the large Swiss cohort study of IBD (SIBDCS) with an emphasis on extraintestinal manifestations demonstrate that up to 25% of patients with IBD have several (up to five) extraintestinal manifestations [27].

The greatest prevalence of extraintestinal manifestations, according to the authors of various countries, was noted in Crohn's disease [24,28,29], in female patients [29,30], in smokers [29,31] and with a longer history of the disease [28].

Among patients with IBD, extraintestinal manifestations were noted in 43.5% of patients with CD and in 23.2% of patients with UC (Fig.10). At the same time, 25% of all patients had more than 1 extraintestinal manifestation. Musculoskeletal extra-intestinal symptoms were observed in 29.2% of patients with CD and 18.4% with UC, and were the leaders in the overall structure of extraintestinal symptoms of IBD (Fig. 11,12).

The most common articular symptom is peripheral polyarthropathy. Meanwhile, the second largest place among articular manifestations is occupied by a more serious

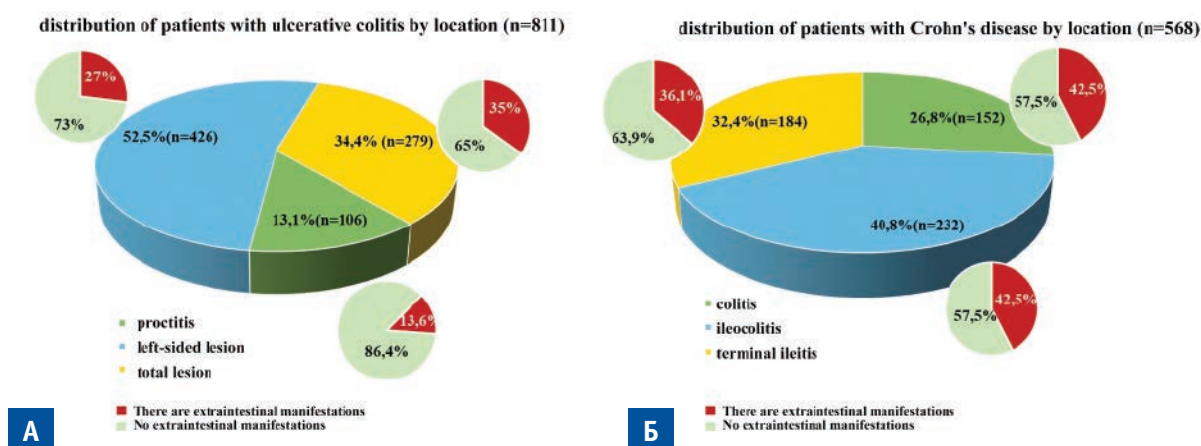


Figure 14. The frequency of detection of extraintestinal manifestations depending on localization of: A) ulcerative colitis; B) Crohn's disease

pathology — ankylosing spondylitis, which is not associated with the IBD activity and can lead to additional disability (Fig.12).

The second place in the incidence was taken by skin manifestations (18.4% and 14.5% in patients with CD and UC, respectively), but at the same time they were 2.5 times more often in patients with CD (8.1%) compared with UC (2.9%). Attention is drawn to the high incidence of ulcerative stomatitis and *erythema nodosum* in patients with CD and relatively the same for other skin manifestations.

Basing on the results of the analysis of the Register data, we were able to establish the dependence in our patients of the incidence of detection of extraintestinal manifestations on the activity of the inflammatory process in the intestine, both in UC and CD (Fig. 13).

Also, in patients with UC, the incidence of extra-intestinal manifestations depended on the extent of the inflammation, with the highest incidence in total UC (35.0%) and the lowest incidence in proctitis (13.6%) (Fig.14A). For CD to date, according to our data, there is no significant difference in the incidence of extraintestinal manifestations depending on the prevalence of CD (Fig.14B).

Treatment for IBD

According to the Register, 94.1% of patients with UC and 57.1% of patients with CD receive therapy with 5-aminosalicylates (5-ASA) in some form and dosage, including for the purpose of cancer prevention. It should be noted that monotherapy with 5-ASA in patients with UC is used in 53% of patients, compared with 24% in CD [32].

Currently, 9.2% of patients receive genetically engineered biological agents. The most commonly used drug is infliximab (48% of all prescriptions), adalimumab is received by 26% of patients, and with approximately the same incidence (8–8.6%) tofacitinib, ustekinumab, vedolizumab. In 100% of patients, biotherapy is usually prescribed after several courses of GCS therapy, which did not lead to the desired response [32].

According to our Register, the incidence of steroid resistance reaches 9.2% of cases, and steroid dependence — 18%. At the time of the data

slice, the incidence of taking immunomodulators was 38% among all observed individuals with IBD, probably affecting the incidence of failures of GCS therapy in the downward direction.

According to the Register, 69.3% of patients needed one or more hospitalizations, and in 15.8% of cases, patients underwent surgery related to IBD. Of course, the incidence of surgery in CD significantly exceeds that in UC (22.7% vs 2.9%) (Fig.15).

Preliminary “Lessons” of Register of IBD Patients

We tried to display schematically potential, in our opinion, problematic “points” of maintaining a unified register of patients with IBD (Fig.16), with a proposal of solutions to hard questions.

The leading position among them is occupied by the fragmentation of existing registers and registries, their absence in many regions, which is caused, among other things, by the complexity of filling in, and the shortage of personnel involved. It is likely that the active introduction of online consultations, the creation of unified questionnaires, the training of nursing staff in the technology of recording information in databases, will facilitate and accelerate the process of filling out registers. In addition, it is possible to involve patients themselves in entering information about the course of their disease in the control sections by creating mobile applications in the form of patient-adapted questionnaires.

CONCLUSION

Data from various registers and publications indicate an increase in the incidence of IBD now, the long time for detection and the difficulties of differential diagnosis emphasize the need to find solutions to problems associated with IBD. It is the clinical registers that allow collecting data on the use of medical technologies and monitoring the results of treatment in real clinical practice. Information about patients with IBD, consolidated into a single Federal Register, will allow to get a complete picture of patients with IBD in the country. In addition,



Figure 16. Potential problem “points” for maintaining a unified Register of IBD patients and ways to overcome them

maintaining the Federal Register and pharmaco-economical evaluation of various treatment methods will optimize treatment costs, ensure rational planning and use of budgetary funds.

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