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# Fatty Acids of Erythrocyte Membranes and Blood Serum in Differential Diagnosis of Inflammatory Bowel Diseases

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**Aim:** to study fatty acid levels in erythrocyte membranes (RBC) and blood serum (BS) in patients with inflammatory bowel diseases (IBDs) to develop differential diagnostic models including fatty acids as biomarkers to distinguish between nosological entities of IBDs (ulcerative colitis — UC, Crohn's disease — CD, unclassified colitis — UCC).

**Materials and methods.** We examined 110 patients (mean age 37,7 ± 12,1 years) with IBDs and 53 healthy patients in control group (43,3 ± 11,7 years). The IBDs group included 50 patients with UC, 41 patients with CD, 19 patients with UCC. An exacerbation of the disease was revealed in 42 patients (84 %) with UC, 34 patients with CD (82.9 %) and 11 people with UCC (57.9 %). The study of fatty acids (FA) composition of RBC membranes and BS was carried out using GC/MS system based on three Agilent 7000B quadrupoles (USA).

**Results.** The most significant for distinguishing active UC from CD exacerbation were serum levels of elaidin ($p$ = 0.0006); docosatetraenoic (n-6) ($p$ = 0.004); docodienic (n-6) ($p$ = 0.009); omega-3/omega-6 ratio ($p$ = 0.02); docosapentaenoic (n-3) ($p$ = 0.03); the sum of eicosapentaenoic and docosahexaenoic ($p$ = 0.03), as well as the content of RBC lauric FA ($p$ = 0.04) (AUC — 0.89, sensitivity — 0.91, specificity — 0.89, diagnostic accuracy — 0.91).

To distinguish active UC from the same of UCC, the following serum FA were found to be significant: alpha-linolenic; saturated (pentadecanoic, palmitic, stearic, arachidic); monounsaturated (palmitoleic, oleic); omega-6 (hexadecadienic, arachidonic) ($p$ = 0.00000011–0.03300000) (AUC — 0.995, sensitivity — 0.98, specificity — 0.96, diagnostic accuracy — 0.97).

The most significant in distinguishing patients with active CD from UCC exacerbation were levels of the following FA: alpha-linolenic; palmitoleic; oleic; the amount of saturated fatty acids (SFA); total unsaturated fatty acids (UFA); stearic; monounsaturated fatty acids (MUFA) amount; SFA/UFA; SFA/PUFA (polyunsaturated fatty acids); linoleic; total PUFA n6; lauric; arachidic acid ($p$ = 0.0000000017–0,030000000) (AUC — 0.914, sensitivity — 0.90, specificity — 0.87, diagnostic accuracy — 0.91).

**Conclusion.** The study of FA levels in groups with different nosological forms of IBDs using complex statistical analysis, including machine learning methods, made it possible to create diagnostic models that differentiate CD, UC and UCC in the acute stage with high accuracy. The proposed approach is promising for the purposes of differential diagnosis of nosological forms of IBDs.

**Keywords:** inflammatory bowel diseases, nosological forms, differential diagnosis, fatty acids, erythrocytes, blood serum

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# Жирные кислоты мембран эритроцитов и сыворотки крови для дифференциальной диагностики воспалительных заболеваний кишечника

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**Цель исследования:** изучить уровни жирных кислот мембран эритроцитов (Эр) и сыворотки крови (СК) у пациентов с воспалительными заболеваниями кишечника для создания дифференциально-диагностических моделей, включающих жирные кислоты в качестве биомаркеров, для различения нозологических форм ВЗК (язвенного колита — ЯК, болезни Крона — БК, неклассифицируемого колита — НКК).

**Материалы и методы.** Обследовано 110 пациентов (средний возраст 37,7 ± 12,1 года) с ВЗК и 53 обследуемых группы сравнения (43,3 ± 11,7 года). Группа пациентов с ВЗК включала в себя больных с ЯК — 50 человек, с БК — 41 человек и 19 пациентов с НКК. У 42 пациентов (84 %) с ЯК, 34 пациентов с БК (82,9 %) и 11 человек с НКК (57,9 %) выявлено обострение заболевания. Исследование состава жирных кислот (ЖК) мембран Эр и СК проведено с помощью ГХ/МС системы на основе трех квадруполей Agilent 7000B (США).

**Результаты.** Наиболее значимыми для различения активного ЯК от обострения БК оказались сывороточные уровни элаидиновой ($p$ = 0,0006), докозатетраеновой (n-6) ($p$ = 0,004), докодиеновой (n-6) ($p$ = 0,009) кислот, отношение омега-3/омега-6 ($p$ = 0,02), докозапентаеновой кислоты (n-3) ($p$ = 0,03); суммы двух омега-3 ПНЖК: эйкозапентаеновой и докозагексаеновой ($p$ = 0,03), а также содержание лауриновой ЖК Эр ($p$ = 0,04) (AUC — 0,89, чувствительность — 0,91, специфичность — 0,89, диагностическая точность — 0,91).

Для различения активного ЯК от стадии обострения НКК оказались значимыми следующие ЖК СК: альфа-линоленовая, насыщенные (пентадекановая, пальмитиновая, стеариновая, арахиновая), мононенасыщенные (пальмитолеиновая, олеиновая), омега-6 (гексадекадиеновая, арахидоновая) (p = 0,00000011–0,03300000), (AUC — 0,995, чувствительность — 0,98; специфичность — 0,96; диагностическая точность — 0,97)..

Наиболее значимыми для различения пациентов с активной БК от обострения НКК оказались уровни ЖК: альфа-линоленовой, пальмитолеиновой, олеиновой, суммы насыщенных жирных кислот (НЖК), суммы ненасыщенных жирных кислот (ННЖК), стеариновой; суммы мононенасыщенных жирных кислот (МНЖК); отношения НЖК/ННЖК; НЖК/ПНЖК (полиненасыщенные жирные кислоты); линолевой; суммы омега-6 ПНЖК; лауриновой; арахиновой ($p$ = 0,0000000017–0,0300000000) (AUC — 0,914, чувствительность — 0,90; специфичность — 0,87, диагностическая точность — 0,91).

**Заключение.** Исследование уровней жирных кислот в группах с разными нозологическими формами ВЗК с помощью комплексного статистического анализа, включая методы машинного обучения, позволило создать диагностические модели, дифференцирующие БК, ЯК и НКК в стадии обострения с высокой точностью. Предложенный подход представляется перспективным для дифференциальной диагностики нозологических форм ВЗК.

**Ключевые слова:** воспалительные заболевания кишечника, нозологические формы, дифференциальная диагностика, жирные кислоты, эритроциты, сыворотка крови

**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.

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## Introduction

According to epidemiological studies, the prevalence of immunoinflammatory diseases is increasing worldwide [1]. The same applies to inflammatory bowel disease, which has increased particularly in the South-Eastern regions of Eurasia, including Russia [2]. The incidence peaks at a young age [3], with a significant reduction in patients' ability to work and quality of life [4], and the phenotypic manifestations of IBDs are extremely polymorphic, making timely diagnosis difficult.

The differential diagnosis of nosological entities in patients with IBDs is now crucial for the individual management of the patient, as each clinical case involves specific therapeutic strategies and prognoses [3, 5, 6]. Nevertheless, non-classical forms of both ulcerative colitis (UC) and Crohn's disease have still been posing a diagnostic problem, since there is no single "gold standard" for the diagnosis of IBDs [5–8]. Therefore, between 5 and 15 % of cases of IBDs do not meet the strict criteria for either UC or CD (9, 10), and in 14 % of patients diagnosed with both UC and CD, the diagnosis can be changed over time [11–13].

An optimisation of standard diagnostic approaches based on clinical features, biomarkers, and the results of traditional radiology, endoscopy and histopathology techniques seems to offer only minor advantages [14, 15]. At the same time, new diagnostic methods in the field of gastrointestinal endoscopy, molecular pathology, genetics, epigenetics, metabolomics and proteomics have already shown promising results [16–22].

Because of the relevance of finding new markers for the differential diagnosis of IBDs, the study of fatty acids seems very promising. Fatty acids, particularly n-3 and n-6 PUFAs, influence important physiological processes, including regulation of gene expression, organisation of inflammation, eicosanoid production, and cell membrane functions [23, 24]. The mechanism by which fatty acids affect the course of IBDs remains incomprehensible [25, 26]. It has been described that n-3 PUFAs contribute to the displacement of arachidonic acid from the cell membrane with a consequent reduction of its derivatives, affect cell membrane protein binding capacity, inhibit NF-κB and reduce its nuclear targeting activity [27, 28], and play an important role in proinflammatory cytokine-induced permeability defects and epithelial barrier dysfunction [29]. According to Masoodi M. et al., elevated levels of specific arachidonic acid metabolites (prostaglandins E2 and D2, thromboxane B2 and hydroperoxyecosatetraenoic acids) used to predict an intestinal inflammation in the colon tissue in ulcerative colitis [30].

**The purpose of this research is as follows:** to study fatty acid levels in erythrocyte membranes (RBC) and blood serum (BS) in patients with inflammatory bowel diseases (IBDs) to develop differential diagnostic models including fatty acids as biomarkers to distinguish between nosological entities of IBDs (ulcerative colitis — UC, Crohn's disease — CD, unclassified colitis — UCC).

## Materials and methods

110 patients (59 women, 51 men, with an average age of 37.7 ± 12.1 years) with IBDs and 53 patients of the comparison group (28 women, 25 men, with an average age of 43.3 ± 11.7 years) have been examined. The group of patients with IBDs has included 50 persons with UC, 41 persons with CD, and 19 patients with unclassified colitis (UCC). The diagnosis has been verified on the basis of a combination of anamnestic data, clinical picture and typical endoscopic and histological changes [7, 8]. The group of patients with inflammatory bowel diseases unclassified included cases where, after review of the medical history, analysis of endoscopic manifestations, histological examination of multiple mucosal biopsies and adequate radiological examination, no exact nosological affiliation of the colitis could be determined [31, 32]. The stage (remission — exacerbation) of the disease has been determined by the combined assessment of clinical, morphological and laboratory parameters [7, 8]. Information on the degree of clinical and morphological activity in the groups is given to assess the comparability of the different nosological entities of IBDs in terms of the severity of the present attack.

As a control group, persons who underwent preventive examination were selected — 53 people leading a healthy lifestyle, drinking alcohol no more than 1–2 times a month in doses not exceeding 20 g per day expressed as pure ethanol, without manifesting pathology of internal organs. The control group was comparable with the main groups by age (mean age 43.3 ± 11.7 years) and gender (28 women and 25 men).

The study has been performed with the approval of the Biomedical Ethics Committee of the Research Institute of Therapy and Preventive Medicine, which is a Branch of the Federal Research Centre Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences (17.12.2018, protocol No. 120). All patients have signed an informed consent to participate in this study.

Patients with IBDs and those in the comparison group have undergone clinical and instrumental examination (history, physical examination, laboratory and instrumental methods according to clinical indications), and the composition and levels of fatty acids (FAs) of erythrocyte membranes and blood serum have been studied.

The study of the composition of fatty acids (FAs) of Er membranes and BS has been performed using a gas chromatography-mass spectrometry (GC/MS) system based on the Agilent 7000B Triple Quadrupole (the USA). The content of fatty acids

has been expressed in relative percentages. The limit of detection of fatty acid is ~ 1 mcg per sample. In addition to the relative content of the selected FAs, the total content of saturated, unsaturated, polyunsaturated, omega-3 PUFAs, omega-6 PUFAs and their ratios have been determined. A detailed description of sample preparation for determining the levels and composition of fatty acids is presented in [33].

Statistical data processing has been performed using the SPSS software, ver. 22. The distribution of quantitative characteristics has been determined by the Kolmogorov–Smirnov test. In the case of a normal distribution, an average value (M) and a standard deviation (SD) have been calculated. The significance of the differences has been assessed by criteria of the Student's *t*-test, and Pearson's test (for a normal distribution). In the absence of a normal distribution, a median (Me), and 25 % and 75 % percentiles (25 %; 75 %) have been calculated, and the reliability of the differences in the values has been assessed using non-parametric test criteria (e.g. Mann–Whitney *U*-test, Kraskell–Wallis test, Pearson's chi-squared test). In all statistical analysis procedures, the critical significance level of the null hypothesis ($p$) has been assumed to be equal to 0.05. Machine learning (Random Forest) computations have been performed using the MATLAB software (R2019a, MathWorks) and the R programming language, using the standard libraries of training classifications and statistical toolkits [34]. The Ortho PLS-DA and Volcano-plot discriminant analysis (a combined method considering the multiplicity of changes and the *t*-test data) have been used to identify fatty acids that are differentiating for different nosological entities of IBDs. The evaluation of the diagnostic accuracy of the models for distinguishing variants of IBDs has been performed using ROC analysis.

## Results

The clinical and instrumental characteristics of the patients of the examined groups are presented in Table 1.

Groups of patients with different nosological entities of IBDs were comparable in age, gender, body mass index, smoking status. Patients with duration of the disease more than 2 years, a relapsing course with moderate severity and moderate clinical, endoscopic activity, have prevailed in all groups. The severity of the exacerbations was comparable between the groups with different nosological entities. Most of the patients were in a state of exacerbation of the disease. The predominant localisation of the process in the colon in CD has determined the relevance of the differential diagnosis of IBDs. Patients with UC and CD were comparable in terms of therapy, with the UCC group having fewer patients using immunomodulators and corticosteroids.

At the time of examination, 42 patients (84 %) with UC, 34 patients with CD (82.9 %) and 11 people with UCC (57.9 %) had an exacerbation; 8 persons (16.0 %) with UC, 7 persons (17.1 %) with CD and 8 patients with UCC (42.1%) were in remission.

The research of the relative content of fatty acids in groups with different nosological entities of IBDs has revealed a certain number of patterns. The total share of saturated fatty acids in erythrocyte membranes and serum was significantly higher in patients with Crohn's disease and ulcerative colitis than in control group and in patients with UCC ($p$ = 0.001–0.025), mainly due to palmitic, stearic and arachic fatty acids. On the contrary, the total content of unsaturated FAs was lower in the CD and UC groups compared to the control group and UCC ($p$ = 0.0009–0.0250), mainly due to monounsaturated FAs and omega-6 PUFAs ($p$ = 0.0004–0.0350), especially in blood serum (Table 2). Ratios of saturated/unsaturated FAs in CD and UC patients were higher than in control group ($p$ = 0.001–0.027) and patients with UCC ($p$ = 0.001–0.012). The index of saturated/polyunsaturated FAs in erythrocyte membranes in patients with UC was higher than in the control group ($p$ = 0.022) (Fig. 1). In patients with CD and UC in blood serum, this indicator was higher than in patients with UCC ($p$ = 0.008, and $p$ = 0.004 respectively) (Table 2).

The greatest differences in levels of Omega-6 PUFAs in the groups studied have been found for hexadecadienoic (C16:2 n-6) and linoleic (C18:2 n-6) PUFAs: in patients with CD and UC, their relative content was lower than in control group and in patients with UCC both in erythrocyte membranes and in blood serum ($p$ = 0.0009–0.045) (Table 2). Patients with UCC have exhibited higher levels of arachidonic acid C20:4 n-6 in erythrocyte membranes compared to the control group ($p$ = 0.07), patients having CD (p = 0.045) and UC patients ($p$ = 0.005) (Fig. 2).

When analysing the omega-3 PUFA, the proportion of the alpha-linolenic omega-3 PUFA (C18:3 n-3) in patients with CD and UC was lower compared to those in the control group ($p$ = 0.00002–0.05000) and patients with UCC ($p$ = 0.00002–0.00200). Elevated levels of eicosapentaenoic acid (C 20:5 n-3) have been detected in erythrocyte membranes in patients with UCC compared to the control group ($p < 0.05$) and to the patients with UC ($p < 0.05$). The level of docozapentaenoic FA (C22:5 n-3) has been higher in the erythrocyte membranes of patients with CD compared with those having UC ($p < 0.05$) (Fig. 3), and in the blood serum has exceeded the values of FA in the control group ($p$ = 0.03) (Table 2).

Since the stage of IBDs has a significant effect on the levels of fatty acids, in groups of patients with IBDs in the acute stage, the spectrum of fatty acids has been analyzed, which can be considered as

*Table 1.* Clinical characteristics of patients with IBDs and control group (M ± SD)

| Characteristics | Control group *n* = 53 (1) | UC patients *n* = 50 (2) | CD patients *n* = 41 (3) | UCC patients *n* = 19 (4) |
|---|---|---|---|---|
| Age (years) | 43.3 ± 11.7 | 35.64 ± 11.03 | 38.64 ± 12.47 | 44.6 ± 13.6 |
| Gender (men/women) | 25/28 | 21/29 | 18/23 | 9/10 |
| Smoking, pers. (%) | 4 (7.5) | 5 (10.0) | 6 (14.6) | 2 (10.5) |
| Body mass index (kg/m$^2$) | 21.9 ± 2.4 | 20.9 ± 3.1 | 20.1 ± 3.9 | 22.0 ± 4.1 |
| *Disease duration* | | | | |
| 0,5–2 years | – | 13 (26.0 %) | 9 (21.9 %) | 9 (47.4 %)*^ |
| Over 2 years | – | 37 (74.0 %) | 32 (78.1 %) | 10 (52.6 %)*^ |
| *The severity of the disease* | | | | |
| Light | – | 7 (14.0 %) | 7 (17.1 %) | 9 (47.4 %)*^ |
| Moderate | – | 32 (64.0 %) | 26 (63.4 %) | 9 (52.6 %) |
| Severe | – | 7 (14.0 %) | 8 (19.5 %) | – |
| *The nature of the course of diseases* | | | | |
| Acute | – | 3 (6.0 %) | 3 (7.3 %) | 5 (26.3 %)*^ |
| Recurrent | – | 43 (86.0 %) | 38 (92.6 %) | 14 (73.7 %)*^ |
| Continuous | – | 4 (8.0 %) | 4 (9.7 %) | – |
| *Stage of the disease* | | | | |
| Exacerbation | – | 42 (84.0 %) | 34 (82.9 %) | 11 (57.9 %)*^ |
| Remission | – | 8 (16.0 %) | 7 (17.1 %) | 8 (42.1 %)*^ |
| *Clinical activity* | | | | |
| Mild | – | 15 (30.0 %) | 10 (24.4 %) | 13 (68.4 %)*^ |
| Moderate | – | 32 (64.0 %) | 26 (63.4 %) | 5 (26.3 %)*^ |
| Severe | – | 3 (6.0 %) | 4 (9.8 %) | 1 (5.3 %) |
| *Endoscopic Activity* | | | | |
| Mild | – | 8 (16.0 %) | 8 (19.5 %) | 9 (47.4 %)*^ |
| Moderate | – | 31 (62.0 %) | 24 (58.5 %) | 9 (47.4 %)*^ |
| Severe | – | 11 (22.0 %) | 9 (21.9 %) | 1 (5.3 %)*^ |
| *Process localization* | | | | |
| Distal colitis | – | 17 (34.0 %) | – | 6 (31.6 %) |
| Left-sided colitis | – | 17 (34.0 %) | – | 6 (31.6 %) |
| Subtotal colitis | – | 3 (6.0 %) | – | 5 (26.3 %) |
| Total colitis | – | 13 (26.0 %) | – | 2 (10.5 %) |
| Large intestine (including rectum) | – | – | 27 (65.8 %) | – |
| Terminal ileitis | – | – | 9 (21.9 %) | – |
| Ileocecal region | – | – | 2 (4.9 %) | – |
| Combined lesion | – | – | 3 (7.3 %) | – |
| Steroid dependence | – | 12 (24.0 %) | 10 (24.4 %) | – |
| Steroid resistance | – | – | 3 (7.3 %) | – |
| *Anemia* | | | | |
| Iron deficiency | – | 32 (64.0 %) | – | 2 (10.5 %)* |
| Inflammatory diseases | – | 1 (2.0 %) | 27(65.9 %)* | – |
| Mixed genesis | – | 6 (12.0 %) | 4 (9.8 %) | – |
| *Therapy* | | | | |
| Aminosalicylates | – | 48 (96.0 %) | 37 (90.2 %) | 16 (84.2 %) |
| Immunomodulators | – | 24 (48.0 %) | 20 (48.7 %) | 4 (21.1 %)*^ |
| Corticosteroids | – | 27 (54.0 %) | 21 (51.2 %) | 5 (26.3 %)*^ |
| No therapy or treatment only with 5-ASA drugs at the time of examination in the acute stage | – | 22 (44.0 %) | 20 (48.7 %) | 10 (52.6 %) |

Note: * — significance of differences from the group of patients with ulcerative colitis, $p < 0.05$; ^ — significance of differences from the group of patients with Crohn's disease, $p < 0.05$.

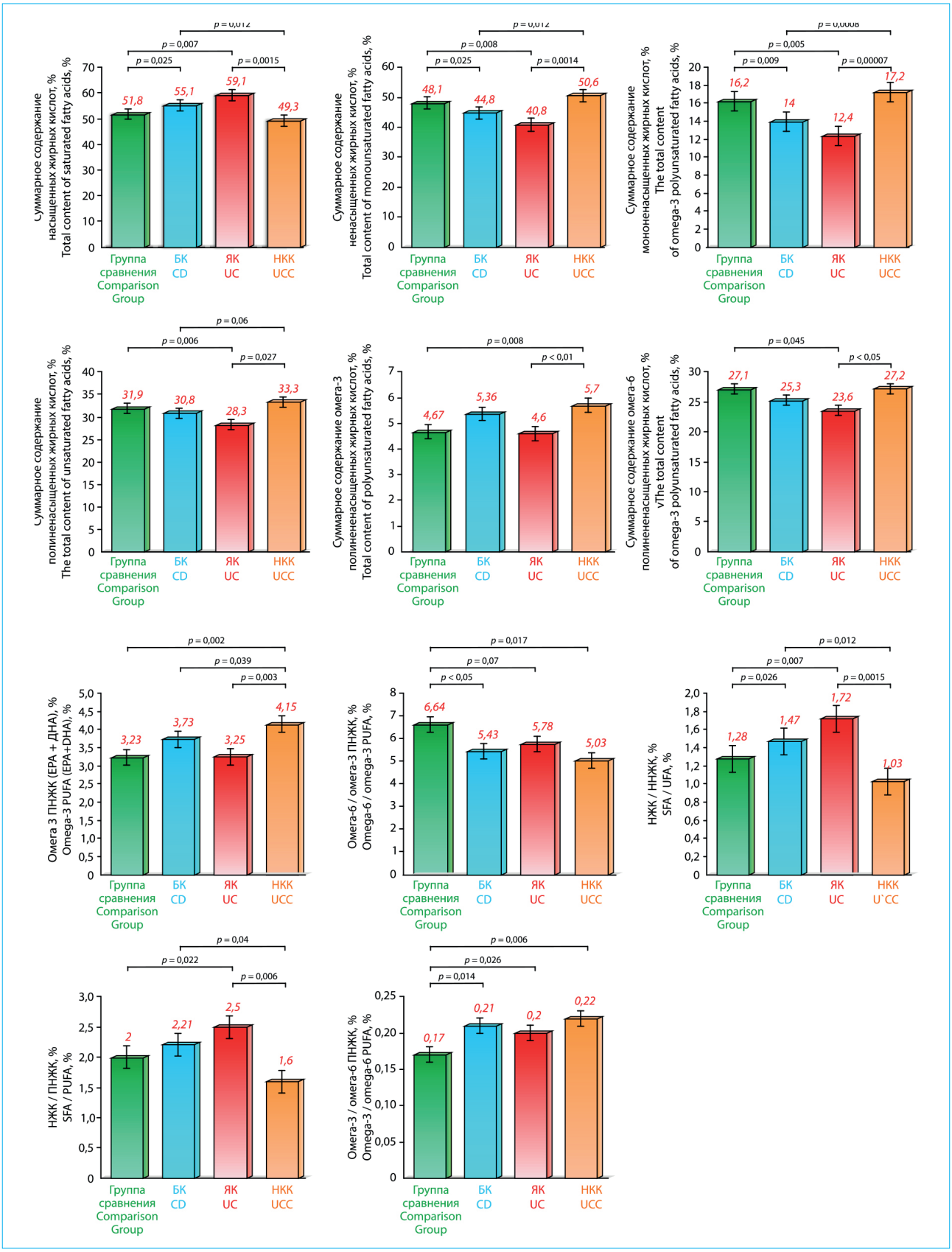


Fig. 1. Total contents and ratios of erythrocyte membrane fatty acids in patients with different nosological forms of IBDs

*Table 2.* Serum fatty acid levels (%) and indices in patients with various nosological forms of IBDs and in the control group (M ± SD), (Me [25 %; 75 %])

| Names, indexes of fatty acids | Control group $n = 53$ (1) | CD patients $n = 41$ (2) | UC patients $n = 50$ (3) | UCC patients $n = 19$ (4) | Mann–Whitney test, $p$ | Kruskal–Wallace test |
|---|---|---|---|---|---|---|
| Saturated FA | 39.40 ± 8.93<br>37.59 [34.34; 43.44] | 46.97 ± 13.25<br>44.72 [36.55; 58.86] | 48.17 ± 12.49<br>46.8 [36.36; 61.22] | 35.06 ± 8.59<br>32.46 [26.89; 40.87] | $p_{1-2} = 0,003$<br>$p_{1-3} < 0,001$<br>$p_{1-4} = 0,06$<br>$p_{2-4} < 0,001$<br>$p_{3-4} < 0,001$ | 0.0001 |
| Unsaturated FA | 60.60 ± 8.93<br>62.41 [56.56; 65.66] | 53.01 ± 13.23<br>55.27 [41.14; 63.44] | 51.81 ± 12.46<br>53.19 [38.78; 63.64] | 64.94 ± 8.59<br>67.54 [59.13; 72.11] | $p_{1-2} = 0,003$<br>$p_{1-3} < 0,001$<br>$p_{1-4} = 0,06$<br>$p_{2-4} < 0,001$<br>$p_{3-4} = 0,0009$ | 0.0001 |
| Monounsaturated FA | 20.08 ± 5.75<br>20.02 [16.02; 23.16] | 17.05 ± 5.54<br>16.74 [12.03; 20.51] | 16.85 ± 5.09<br>16.67 [13.28; 21.34] | 24.84 ± 6.28<br>23.07 [18.78; 27.77] | $p_{1-2} = 0,007$<br>$p_{1-3} = 0,035$<br>$p_{1-4} = 0,038$<br>$p_{2-4} = 0,0004$<br>$p_{3-4} = 0,0015$ | 0.0005 |
| Polyunsaturated FA | 40.42 ± 8.35<br>40.99 [34.59; 47.34] | 35.96 ± 9.05<br>36.49 [27.13; 44.44] | 34.98 ± 9.28<br>35.31 [26.65; 42.67] | 40.60 ± 7.96<br>40.39 [36.16; 48.55] | $p_{1-2} = 0,015$<br>$p_{1-3} = 0,002$<br>$p_{2-4} = 0,07$<br>$p_{3-4} = 0,03$ | 0.0051 |
| Omega 3 PUFA | 2.37 ± 1.74<br>2.02 [1.22; 2.76] | 2.97 ± 1.65<br>2.5 [1.8; 3.95] | 2.42 ± 1.20<br>2.06 [1.53; 2.81] | 2.63 ± 1.23<br>2.29 [1.63; 3.08] | $p_{1-2} = 0,038$ | 0.1585 |
| C18:3;6,9,12 (n-3) Octadecadienic *(α-Linolenic)* | 0.24 ± 0.18<br>0.19 [0.09; 0.33] | 0.11 ± 0.11<br>0.07 [0.05; 0.14] | 0.12 ± 0.11<br>0.09 [0.04; 0.19] | 0.30 ± 0.14<br>0.27 [0.23; 0.38] | $p_{1-2} = 0,00002$<br>$p_{1-3} = 0,0007$<br>$p_{1-4} = 0,07$<br>$p_{2-4} = 0,00002$<br>$p_{3-4} = 0,0002$ | 0.00001 |
| C20:5;5,8,11,14,17 (n-3) *(Eicosapentaenoic)* | 0.55 ± 0.84<br>0.33 [0.19; 0.66] | 0.64 ± 0.56<br>0.39 [0.25; 0.86] | 0.46 ± 0.30<br>0.34 [0.17; 0.52] | 0.62 ± 0.57<br>0.46 [0.24; 0.62] | $p_{2-3} < 0,05$ | 0.2887 |
| C22:5;7,10,13,16,19 (n-3) *(Docosapentaenoic)* | 0.32 ± 0.28<br>0.28 [0.17; 0.39] | 0.42 ± 0.24<br>0.35 [0.27; 0.49] | 0.35 ± 0.28<br>0.28 [0.21; 0.44] | 0.33 ± 0.21<br>0.28 [0.22; 0.40] | $p_{1-2} = 0,03$ | 0.1735 |
| Omega 3 PUFA (EPA+DHA) | 1.82 ± 1.54<br>1.59 [0.86; 2.22] | 2.44 ± 1.51<br>1.89 [1.36; 3.32] | 1.95 ± 1.05<br>1.59 [1.2; 2.39] | 2.00±1.08 | $p_{1-2} = 0,027$ | 0.1426 |
| Omega 6 PUFA | 37.95 ± 8.29<br>38.41 [32.42; 44.11] | 32.93 ± 8.97<br>33.66 [24.53; 40.99] | 32.51 ± 8.86<br>32.38 [25.64; 39.05] | 37.79 ± 8.00<br>36.46 [32.52; 46.08] | $p_{1-2} = 0,009$<br>$p_{1-3} = 0,0019$<br>$p_{2-4} = 0,07$<br>$p_{3-4} = 0,037$ | 0.004 |
| C16:2;9,12 (n-6) Hexadecadienoic | 0.10 ± 0.08<br>0.08 [0.03; 0.16] | 0.06 ± 0.07<br>0.03 [0.01; 0.08] | 0.07 ± 0.1<br>0.02 [0.01; 0.07] | 0.19 ± 0.27<br>0.11 [0.05; 0.21] | $p_{1-2} = 0,004$<br>$p_{1-3} = 0,006$<br>$p_{2-4} = 0,0016$<br>$p_{3-4} = 0,003$ | 0.0006 |
| C18:2;9,12 (n-6) Octadecadienoic *(Linoleic)* | 32.04 ± 7.79<br>32.44 [26.01; 37.17] | 26.44 ± 7.62<br>26.04 [18.93; 33.32] | 26.72 ± 8.06<br>26.75 [19.65; 32.09] | 31.11 ± 7.58<br>29.32 [25.60; 39.93] | $p_{1-2} = 0,0009$<br>$p_{1-3} < 0,001$<br>$p_{2-4} = 0,045$<br>$p_{3-4} = 0,08$ | 0.0014 |
| C20:4;5,8,11,14 (n-6) *(Eicosatetraenoic, arachidonic)* | 4.72 ± 1.84<br>4.41 [3.41; 5.67] | 5.17 ± 1.82<br>4.75 [3.82; 6.20] | 4.63 ± 1.44<br>4.43 [3.59; 5.50] | 5.58 ± 1.73<br>6.20 [3.64; 7.19] | $p_{3-4} = 0,043$ | 0.1797 |
| Omega 6/ Omega 3 PUFA | 22.18 ± 15.49 | 14.37 ± 8.46 | 16.05 ± 8.27 | 17.33 ± 7.70 | $p_{1-2} = 0,014$<br>$p_{1-3} = 0,048$ | 0.0537 |
| Saturated / Unsaturated FA | 0.70 ± 0.36 | 1.04 ± 0.67 | 1.06 ± 0.56 | 0.58 ± 0.26 | $p_{1-2} = 0,004$<br>$p_{1-3} < 0,001$<br>$p_{1-4} = 0,07$<br>$p_{2-4} = 0,0015$<br>$p_{3-4} = 0,001$ | 0.0001 |
| Saturated / Polyunsaturated FA | 1.07 ± 0.54 | 1.53 ± 0.97 | 1.58 ± 0.85 | 0.94 ± 0.42 | $p_{1-2} = 0,008$<br>$p_{1-3} = 0,0015$<br>$p_{2-4} = 0,008$<br>$p_{3-4} = 0,004$ | 0.0006 |
| Omega 3/ Omega 6 PUFA | 0.06 ± 0.05 | 0.14 ± 0.29 | 0.08 ± 0.04 | 0.07 ± 0.04 | $p_{1-2} = 0,002$<br>$p_{1-3} = 0,009$ | 0.0101 |

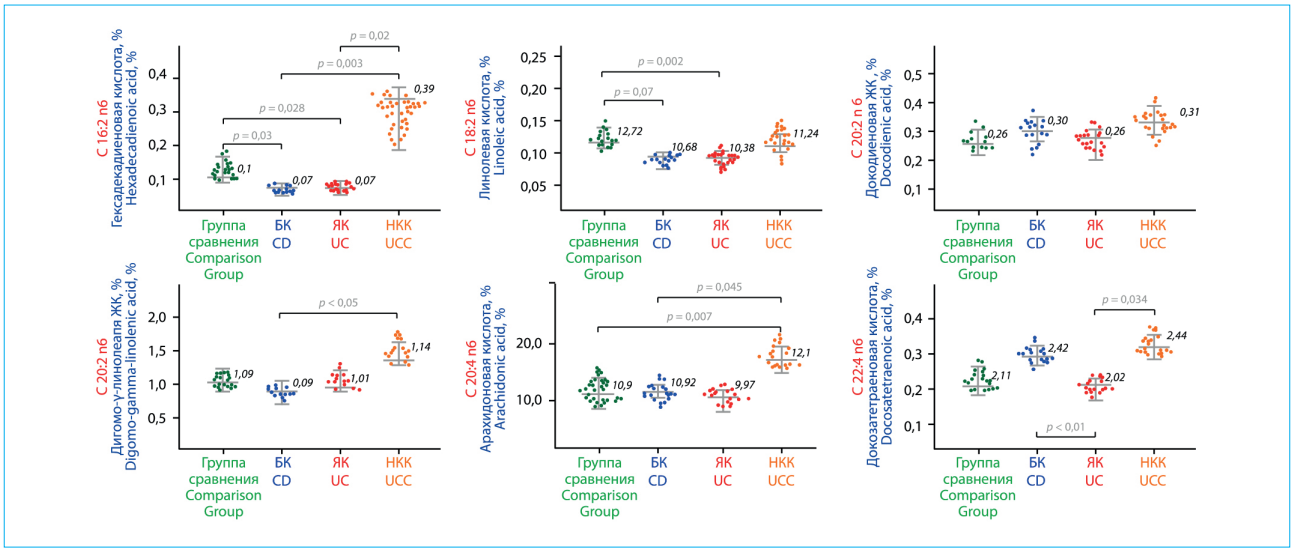


Fig. 2. Relative levels of omega 6 PUFA of erythrocyte membranes in patients with different nosological forms of IBDs

biomarkers for distinguishing nosological entities of IBDs during the period of their activity.

Before the subsequent stages of statistical analysis, the indicators of the relative fatty acid content of erythrocyte membranes and blood serum have become normalized (Fig. 4).

The performed discriminant analysis, namely the Ortho PLS-DA in patients with UC and acute CD (Fig. 5) has revealed the presence of FAs, which are significant in discriminating between these nosological entities of IBDs during their activity period. The Random Forest analysis has determined the degree of influence of fatty acid levels on the differentiation of active UC and CD. In descending order of importance of FAs and their sums have been distributed as follows: C18:1;c9, C12:0, C18:0, C14:0, C22:4 n-6, the total contents of unsaturated FAs, monounsaturated, saturated FAs, C15:0, C16:1;9, saturated FAs / unsaturated FAs, C16:2 n-6, the sum of Omega-6 PUFA, C20:4n-6, C20:0.

Table 3 presents data obtained using the Volcano-plot analysis method, revealing fatty acids that should be considered as biomarkers for distinguishing active UC and CD.

According to the data in Table 3, serum levels of elaidic ($p$ = 0.0006) were the most significant for distinguishing active ulcerative colitis from exacerbations of Crohn's disease, docosatetraenoic (n-6) ($p$ = 0.004), docodienoic (n-6) ($p$ = 0.009), omega-3/omega-6 ratio ($p$ = 0.02), docosapentaenoic (n-3)

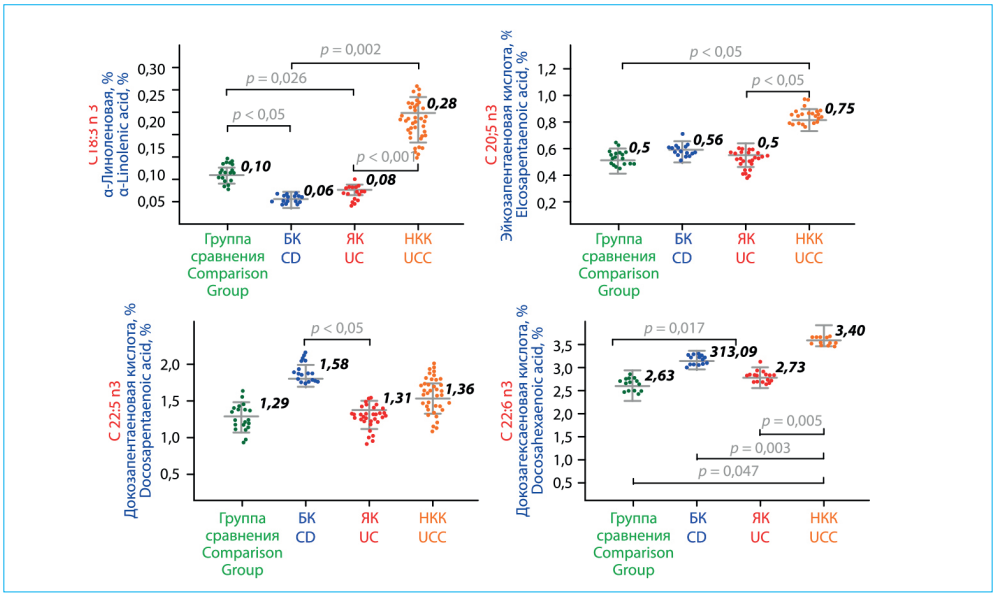


Fig. 3. Relative levels of omega 3 PUFAs of erythrocyte membranes in patients with different nosological forms of IBDs

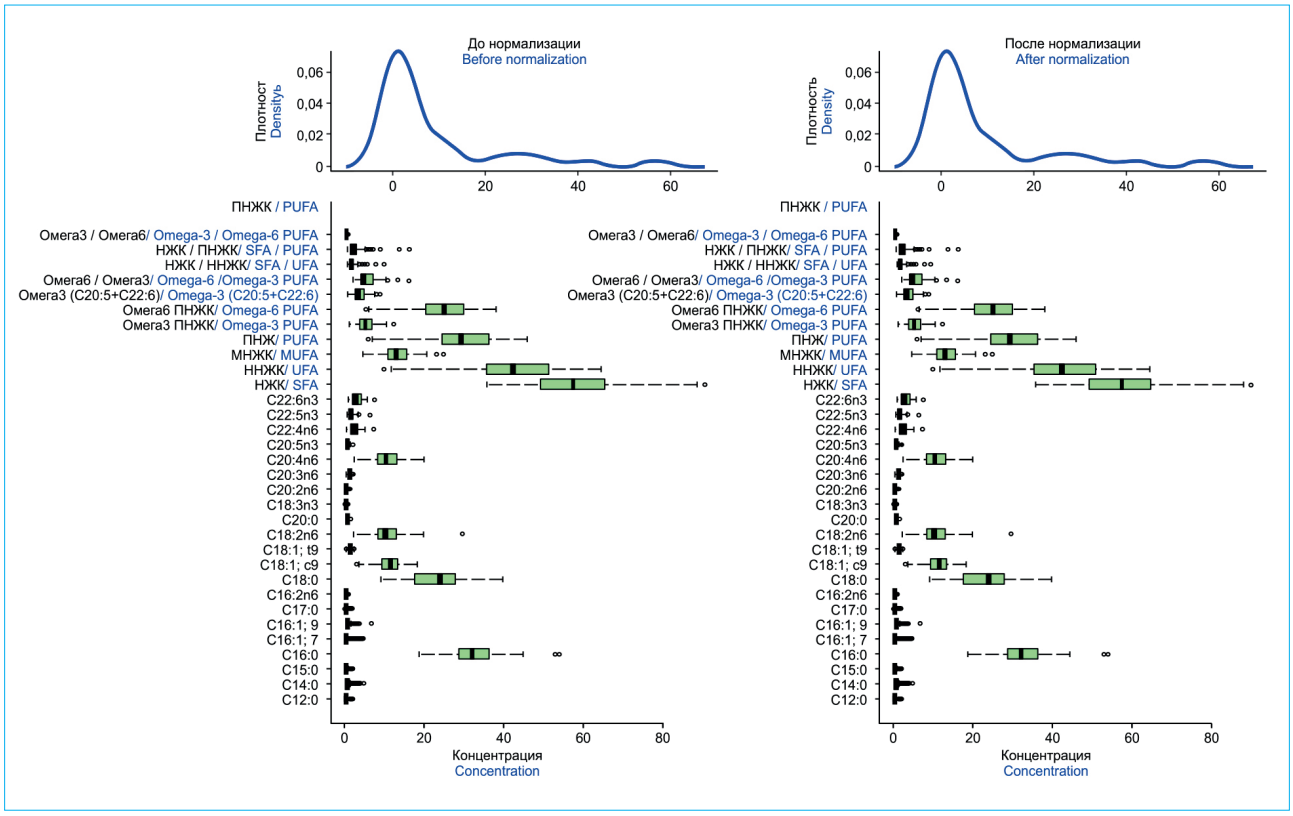


Fig. 4. Normalization of indicators of the relative content of fatty acids in erythrocyte membranes. Note: the figure on the left shows the FA levels before normalization, on the right — after normalization

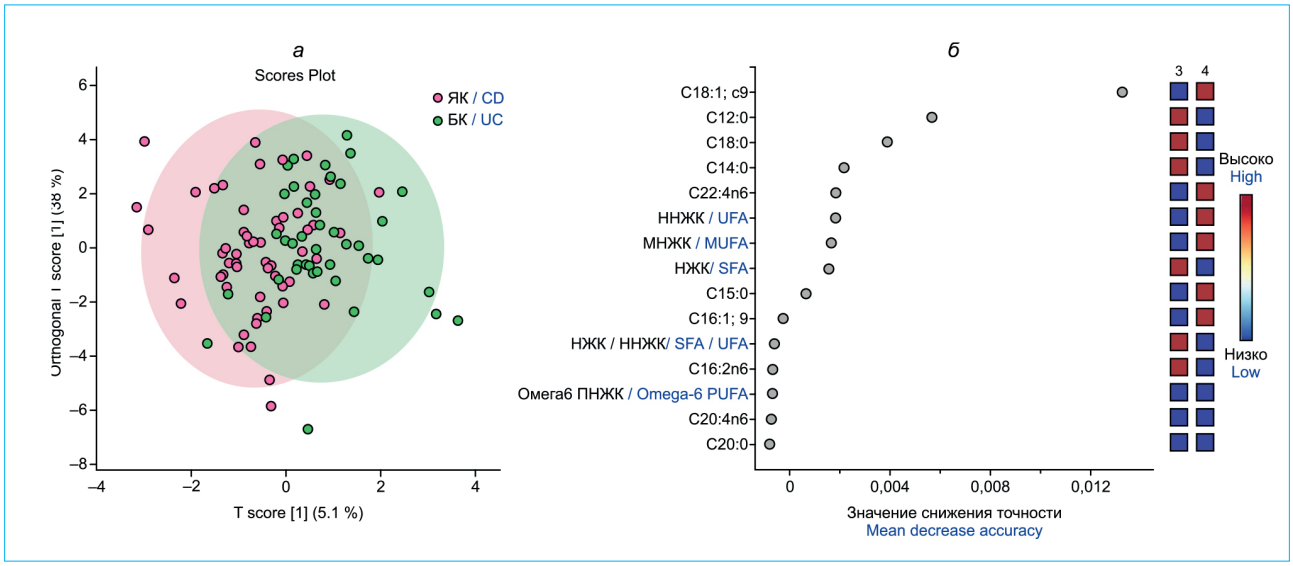


Fig. 5. Ortho PLS-DA fatty acid analysis of erythrocyte and serum membranes (left) and Random Forest analysis to establish the degree of significance of FAs (right) to distinguish between active UC and CD

($p = 0.03$), sum of two omega-3 PUFAs, eicosapentanoic and docosahexaenoic ($p = 0.03$), as well as the percentage of lauric acid content of erythrocyte membranes ($p = 0.04$). The percentage of eicosapentaenoic acid and the total proportion of omega-3 PUFA in blood serum should also be considered as potential biomarkers, since the degree of their significance for distinguishing CD and UC in the acute stage shall increase with incrementing the number of examined persons.

The model created from the list of the above-described FAs has showed high levels of diagnostic accuracy in distinguishing active UC and CD (Fig. 6) with AUC 0.89; sensitivity 0.91; specificity 0.89; diagnostic accuracy 0.91).

*Table 3.* Serum and erythrocyte membrane fatty acids — biomarkers for distinguishing UC from CD in the acute stage (Volcano-plot method)

| Name of fatty acids | Fold change (FC) | $\log_2$ (FC) | *p* | $-\log_{10}(p)$ |
|---|---|---|---|---|
| *Serum fatty acids* | | | | |
| C18:1;t9 Trans-9-octadecanoic *(Elaidic)* | 0.71021 | –0.49368 | 0.00062 | 3.2075 |
| C22:4;7,10,13,16 (n-6) *(Docosatetraenoic)* | 0.60614 | –0.72227 | 0.004128 | 2.3842 |
| C20:2;11,14 (n-6) *(Docodienic)* | 0.76247 | –0.39126 | 0.009541 | 2.0204 |
| Omega 3/ Omega 6 PUFA | 0.7328 | –0.44851 | 0.02333 | 1.632 |
| C22:5;7,10,13,16,19 (n-3) *(Docosapentaenoic)* | 0.68376 | –0.54845 | 0.03222 | 1.4919 |
| Omega 3(EPA + DHA) PUFA | 0.78695 | –0.34566 | 0.037886 | 1.4215 |
| C20:5;5,8,11,14,17 (n-3) *(Eicosapentaenoic)* | 0.70808 | –0.49801 | 0.067811 | 1.1687 |
| Omega 3 PUFA | 0.64182 | –0.63976 | 0.08240 | 1.0841 |
| *Fatty acids of erythrocyte membranes* | | | | |
| C12:0 Dodecanoic (Lauric) | 2.5157 | 1.331 | 0.04528 | 1.3441 |

The relative fatty acid values in the other pair of groups, namely patients with ulcerative colitis and unclassified colitis, have been subjected to the statistical processing sequence as described above.

To distinguish active UC from the acute stage of UCC, the following serum FAs were significant: alpha-linolenic acid, the content of saturated acids (pentadecanoic, palmitic, stearic, arachine), monounsaturated acids (palmitoleic, oleic), omega-6 (hexadecadiene, arachidonic) acids ($p$ = 0.00000011–0.03300000) (Table 4).

The ROC analysis performed using the levels of even individual FAs — alpha-linolenic, palmitoleic, stearic — made it possible to distinguish active UC from UCC in the acute stage with high accuracy (the areas under the AUC curve are 0.873; 0.886; 0.851, respectively) (Fig. 7).

The diagnostic accuracy of the panel (data obtained using the Random Forest Classifier method and ROC analysis), consisting of a set of fatty acids (Table 4), turned out to be higher than when using individual FAs, when distinguishing patients with active UC from patients with acute UCC (Fig. 8) with AUC 0.995; sensitivity 0.98; specificity 0.96; diagnostic accuracy 0.97).

The Volcano-plot method has been used to obtain a list of serum FAs that meet the requirements of biomarkers to distinguish a pair of groups — patients with exacerbation of CD and exacerbation of UCC. The levels of the following FAs have been the most significant for distinguishing patients with active CD from exacerbation of UCC: alpha-linolenic, palmitoleic, oleic, the sum of saturated FAs, the sum of unsaturated FAs, stearic acid, the sum of monounsaturated FAs (MUFAs), the ratio of saturated / unsaturated FAs, saturated FAs / PUFAs, linoleic acid, the sum of omega-6 PUFA, lauric, arachidic acids (Table 5) ($p$ = 0.0000000017–0.0300000000). Margaric and myristic fatty acids,

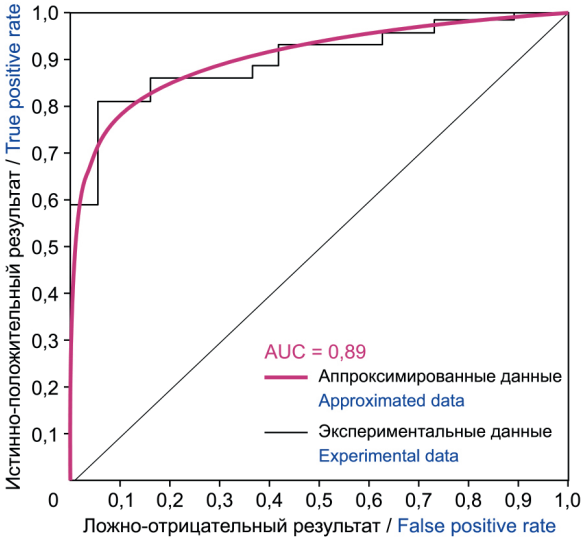


Fig. 6. ROC-curve for assessing the accuracy of distinguishing ulcerative colitis in the acute stage from active Crohn's disease

with an increase in the number of observations, can also be considered biomarkers for distinguishing active CD from UCC in the acute stage. The Ortho PLS-DA method has showed the presence of differentiating FAs, distinguishing active CD from UCC in the acute stage (Fig. 9). The ROC analysis using levels of 5 FAs (alpha-linolenic, palmitoleic, oleic, sum of saturated FAs, sum of unsaturated FAs) has allowed us to achieve high accuracy in distinguishing active CD from exacerbation of UCC — the area under the curve is equal to 0.914 (Fig. 10). The sensitivity of the created model was 0.90; specificity — 0.87; diagnostic accuracy — 0.91).

*Table 4.* Serum fatty acids — biomarkers for distinguishing active UC from active NCC (Volcano-plot method)

| Name of fatty acids | Fold change (FC) | $\log_2$(FC) | *p* | $-\log_{10}(p)$ |
|---|---|---|---|---|
| C18:3;6,9,12 (n-3) Octadecadienoic *(α-Linolenic)* | 2.7509 | 1.4599 | 1.13E-07 | 6.9469 |
| C16:1;9 Cis-9-hexadecanoic *(Palmitoleic)* | 2.117 | 1.082 | 1.72E-07 | 6.7651 |
| Total content of monounsaturated fatty acids | 1.4963 | 0.5814 | 2.72E-07 | 6.5658 |
| C18:1;c9 Cis-9-octadecanoic *(Oleic)* | 1.5023 | 0.5871 | 6.09E-07 | 6.2152 |
| C18:0 Octadecanic *(stearic)* | 0.4646 | –1.1059 | 8.44E-06 | 5.0735 |
| Total content of unsaturated fatty acids | 1.2863 | 0.3632 | 4.39E-05 | 4.3575 |
| The total content of saturated fatty acids | 0.7083 | –0.4974 | 4.70E-05 | 4.3277 |
| SFA/UFA | 0.5148 | –0.9579 | 0.00032 | 3.489 |
| C15:0 Pentadecanoic | 1.4803 | 0.5659 | 0.00076 | 3.1149 |
| C16:0 Hexadecanic *(Palmitic)* | 0.8216 | –0.2834 | 0.00077 | 3.1121 |
| SFA/PUFA | 0.5599 | –0.8366 | 0.00139 | 2.8545 |
| C20:0 *(Eicosanoic, Arachic)* | 0.5334 | –0.9066 | 0.00144 | 2.8416 |
| C14:0 Tetradecanoic *(Myristic)* | 1.3901 | 0.47514 | 0.00502 | 2.299 |
| C16:1;7 cis-7-hexadecanoic *(7-Palmitoleic)* | 1.5857 | 0.66511 | 0.00569 | 2.2448 |
| C16:2;9,12 (n-6) Octadecadienoic | 2.6124 | 1.3854 | 0.012297 | 1.9102 |
| C17:0 Heptadecanoic *(Margaric)* | 1.2486 | 0.32028 | 0.02423 | 1.6155 |
| C12:0 Dodecanoic *(Lauric)* | 1.9624 | 0.97265 | 0.02937 | 1.5321 |
| C20:4;5,8,11,14 (n-6) *(Eicosatetraenoic, arachidonic)* | 1.2099 | 0.27486 | 0.03379 | 1.4711 |

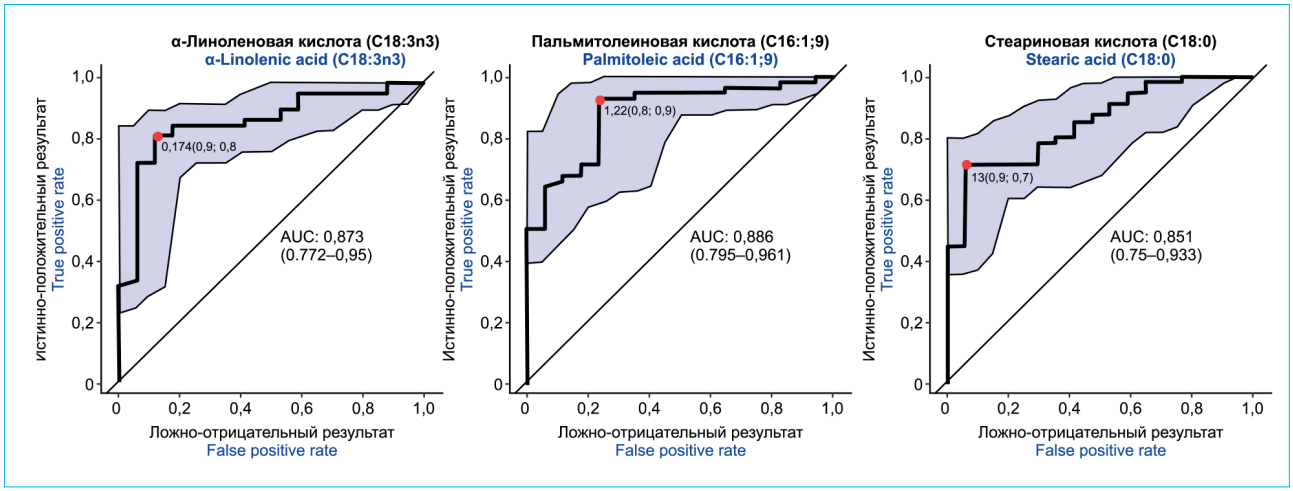


Fig. 7. ROC-analysis using the level of individual fatty acids — alpha-linolenic, palmitoleic, stearic to distinguish between active UC and UCC

A comparison of the list of fatty acids that are differentiating between active UC and UCC and exacerbation of CD and UCC has led to the conclusion that some of the FAs in the diagnostic models has overlapped — these are for example alpha-linolenic, palmitoleic, oleic, stearic, lauric, arachidic acids, total contents of fatty acids, saturated FAs, unsaturated FAs, MUFAs, ratio of saturated / unsaturated FAs, saturated FAs / PUFAs. However, the degree of significance of these fatty acid levels, total contents and ratios have differed from model to model. In addition, it was possible to identify FAs that were found to be associated with only one particular model each: For the model "active UC vs. active UCC" they are pentadecane, palmitic acids, 7-palmitooleic, hexadecadienoic and arachidonic acids; for the model to distinguish between exacerbation of CD and UCC

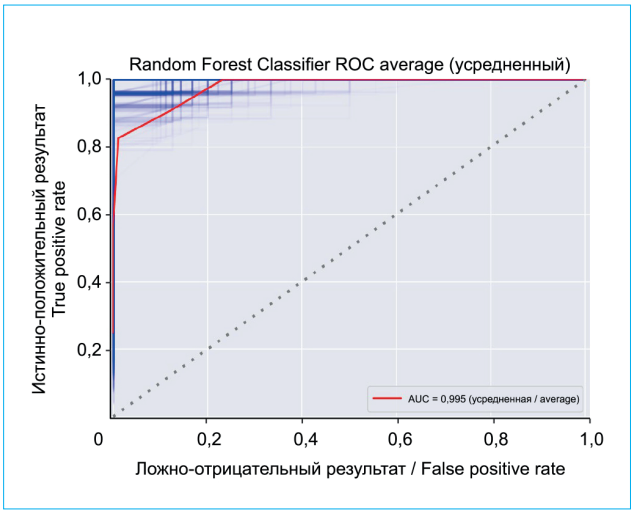


Fig. 8. Diagnostic accuracy of a model based on the use of a list of serum FAs to distinguish between active UC and UCC in the acute stage

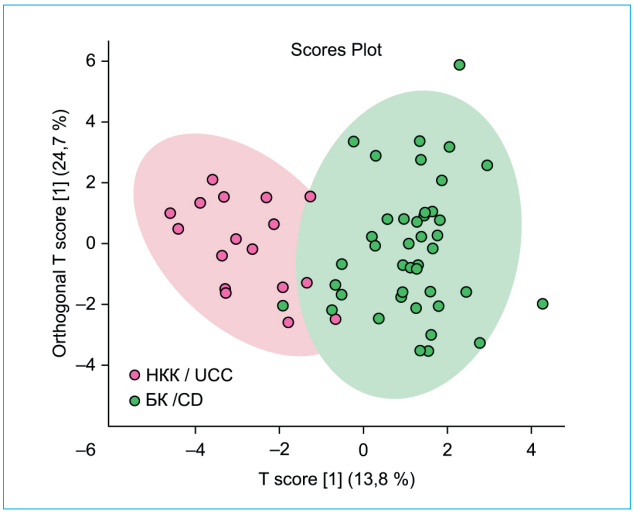


Fig. 9. Ortho PLS-DA method for distinguishing a CD exacerbation from an active UCC

they are as follows: the levels of linoleic acid and total content of omega-6 PUFA in blood serum.

## Discussion

In recent years, there was an increased interest in metabolomics research, including in patients with inflammatory bowel diseases, to elucidate the pathogenetic mechanisms of IBDs and to improve their diagnostic techniques [35]. Metabolomics performs an analytical description of complex biological samples and is aimed at characterizing and quantifying all small molecules involved in the process, thereby revealing unique chemical "fingerprints" that leave behind specific cellular processes [36].

The results published in a number of papers convincingly exhibit a high potential of this approach in the differential diagnosis of nosological entities of IBDs. For example, H.R. Williams et al. have performed serum metabolic profiling in CD patients, UC patients and healthy individuals using 1H NMR spectroscopy. Using partial discriminant least squares analysis with orthogonal signal correction, the authors showed significant differences in lipid and choline metabolism between CD and UC [37].

Hisamatsu et al. have studied the amino acid profiles of plasma associated with IBDs. A multidimensional

*Table 5.* Serum fatty acids — biomarkers for distinguishing active CD from active UCC

| Name of fatty acids | Fold change (FC) | $\log_2$(FC) | *p* | $-\log_{10}(p)$ |
|---|---|---|---|---|
| C18:3;6,9,12 (n-3) Octadecadienoic *(α-Linolenic)* | 0.32785 | –1.6089 | 1.74E-09 | 8.7601 |
| C16:1;9 Cis-9-hexadecanoic *(Palmitoleic)* | 0.51831 | –0.94811 | 1.78E-05 | 4.75 |
| C18:1;c9 Cis-9-octadecanoic *(Oleic)* | 0.66396 | –0.59083 | 2.34E-05 | 4.6302 |
| The total content of saturated fatty acids | 1.3968 | 0.48217 | 0.000202 | 3.6943 |
| Total content of unsaturated fatty acids | 0.78309 | –0.35274 | 0.000209 | 3.6795 |
| C18:0 Octadecanic *(Stearic)* | 1.9976 | 0.99829 | 0.000275 | 3.5605 |
| Total content of monounsaturated fatty acids | 0.7196 | –0.47474 | 0.000842 | 3.0746 |
| SFA/UFA | 1.9051 | 0.92984 | 0.004279 | 2.3686 |
| SFA/PUFA | 1.7575 | 0.81353 | 0.007424 | 2.1293 |
| C18:2;9,12 (n-6) Octadecadienic *(Linoleic)* | 0.80084 | –0.32042 | 0.012725 | 1.8953 |
| Total content of omega 6 PUFA | 0.82064 | –0.28517 | 0.014299 | 1.8447 |
| C12:0 Dodecanoic *(Lauric)* | 0.5069 | –0.98023 | 0.022351 | 1.6507 |
| C20:0 *(Eicosanoic, Arachic)* | 1.6447 | 0.71779 | 0.034753 | 1.459 |
| C17:0 Heptadecanoic *(Margaric)* | 0.80203 | –0.31828 | 0.06724 | 1.1724 |
| C14:0 Tetradecanoic *(Myristic)* | 0.77607 | –0.36575 | 0.071056 | 1.1484 |

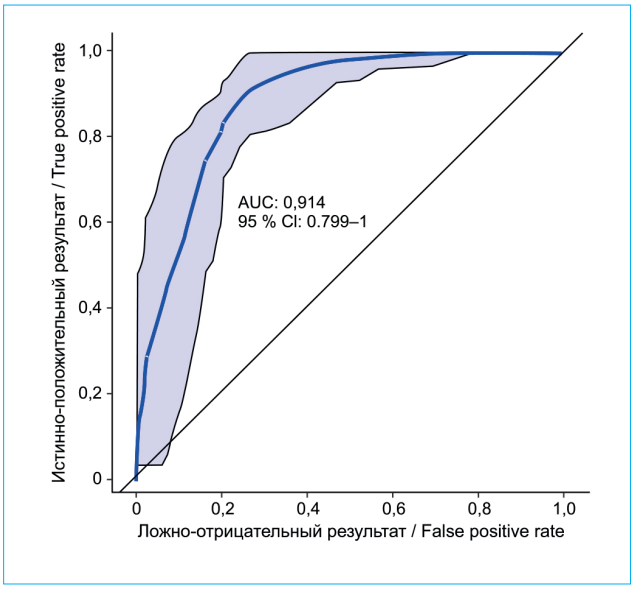


Fig. 10. ROC analysis using levels of 5 fatty acids — alpha-linolenic, palmitoleic, oleic, total SFA, total UFA — to distinguish between a CD exacerbation and active UCC

index constructed from the plasma aminogram, including histidine and tryptophan, has showed considerable accuracy in distinguishing between CD and UC [38]. Another group of researchers using gas chromatography-mass spectrometry has reported that the content of amino acids and molecules associated with the tricarboxylic acid cycle (TCA) in blood serum had differed in patients with ulcerative colitis and healthy persons, as well as in groups of patients with UC and CD [39].

E.A. Scoville et al. have examined serum metabolite profiles using high-performance liquid chromatography-mass spectrometry and identified 173 altered metabolites including lipids, amino acids and TCA metabolites in patients with IBDs compared to healthy subjects. While a significant change in 286 serum metabolites has been found in patients with CD compared to healthy individuals, in patients with UC, a decrease in the level of only five metabolites has been found. The metabolism of fatty acids, acylcarnitine metabolites, sphingolipids and bile acids has differed significantly in patients with CD compared to patients with UC and control groups of healthy subjects [40]. The profiles of serum metabolites also have differed in children with CD and UC [41]. Taken together, these studies show that serum metabolic profiling is promising for differentiating subtypes of IBDs.

In the previous pilot study — on small groups of patients with IBDs, we have showed the presence of differences in the relative content of FAs depending on the nosological entity of IBDs [42], which has been confirmed by other authors as well [26, 40, 43]. The data on fatty acid profiles in patients with IBDs obtained in this study are not fully consistent with the results of similar studies, which may be due to differences in ethnicity, gender and age composition of patient groups, differences in the nosological entities of IBDs, the therapy used, the use of different biological samples for analysis, and the characteristics of sample preparation [44–46].

Due to the many factors that could affect the levels of the studied FAs, normalization of the studied indicators has been carried out before the start of statistical processing. This turned out to be significant when distinguishing nosological entities of IBDs in the acute stage. The use of the Student's t-test and the method of main components in modification (Ortho PLS-DA) made it possible to clearly identify differences in the studied pairs of groups. The Volcano-plot method has provided identification of parameters claiming to be biomarkers in the process of differentiation between different groups of patients with IBDs (CD–UC, CD–UCC, UC–UCC). These approaches are well-founded and widely used in metabolomics [34, 47].

The list of fatty acids, the relative content of which differs in patients with different variants of IBDs, without taking into account the stage of the disease, turned out to be different compared to the analysis of the fatty acid profile in patients with active IBDs. This circumstance is due to the close relationship of the composition and levels of fatty acids of erythrocyte membranes and blood serum with the stage of the disease [48].

When analysing the spectrum of fatty acids in patients with CD, UC, and UCC separately and taking into account the stage of the disease, markers associated with individual nosological forms of IBDs have been identified. Subsequently, it seems promising to compare the fatty acid profiles of serum and erythrocyte membranes with the "pattern" of FAs' intestinal tissues of patients with IBDs.

Taking into account the stage of IBDs, the serum levels of elaidic ($p = 0.0006$), docosatetraenoic (n-6) ($p = 0.004$), docodeinic (n-6) ($p = 0.009$), omega-3/omega-6 ratio ($p = 0.009$) were the most significant for differentiating patients with UC and patients with CD 0.02), eicosapentaenoic (n-3) ($p = 0.03$), the sum of two omega-3 PUFAs — eicosapentaenoic and docosahexaenoic ($p = 0.03$), as well as the content of lauric FA of the membranes of erythrocytes ($p = 0.04$). At the same time, in patients with Crohn's disease, the proportion of unsaturated FAs mainly increased, and the content of saturated lauric acid was higher in ulcerative colitis. It is known that the fatty acid composition of vital cell membranes is maintained through the activity of desaturases involved in the metabolism of PUFAs, which are usually controlled by the principle of substrate regulation [49]. It has been shown that in patients with acute CD, the regulation of PUFAs' desaturation is disrupted to a greater extent than in UC [40, 43]. Therefore, with an exacerbation of UC, unlike CD, the levels of the end products of the metabolic cascade of fatty

acids (omega-3 PUFA, omega-3/omega-6 ratio) are reduced with an increased content of saturated FAs. Probably, dietary recommendations to increase omega-3 PUFA and limit foods containing saturated fats are important for maintaining remission in ulcerative colitis. Data from Uchiyama K. et al. has demonstrated the importance of maintaining an omega-3/omega-6 index of more than 0.65 for patients with UC. The same authors have showed that Japanese patients with UC remained in remission of the disease with an omega-3/omega-6 index equal to one [43]. Different levels of the omega-6/omega-3 ratio in patients with UC and CD, as well as the possible pathogenetic value of this index in different nosological entities of IBDs have been noted by E. Scaioli et al. [44].

T.A. Seimon et al. [50] have reported that saturated fatty acids may contribute to macrophage inflammation and lipotoxicity. The increased toxicity of saturated FAs may be to some extent due to the fact that they are less effectively esterified into triglycerides. Although the mechanisms underlying lipotoxicity are currently unknown, the accumulation of palmitic acid in macrophages may be related to inflammation [51]. It can be assumed that this mechanism is implemented in patients with UC due to the increased level of saturated FAs.

D.M. Wiese et al. have found that serum fatty acids correlated with the levels of proinflammatory cytokines in the colon in patients with ulcerative colitis [52]. E.A. Scoville et al. have proved some associations of serum fatty acid levels in patients with Crohn's disease with serum cytokines and disease activity [53]. The profiles of significant cytokines and adiponectins in different variants of IBDs have differed, which may explain the different lists of serum fatty acids significant for CD and UC, and can be used for differential diagnosis.

The list of a number of fatty acids (alpha-linolenic, palmitoleic, oleic, the sum of saturated FAs, the sum of unsaturated FAs, stearic, the sum of monounsaturated FAs, the ratio of saturated FAs / unsaturated FAs, saturated FAs / PUFAs) to distinguish active UC and CD from the stage of exacerbation of UCC turned out to be similar. The significance of other FAs, mainly saturated, linoleic and the sum of omega-6 PUFAs, for distinguishing between CD–UCC and UC–UCC pairs was not the same. It can be assumed that this circumstance indirectly reflects the heterogeneity of patients with unclassified colitis. The coincidence of the presence of linoleic and palmitic acid levels in the models presented is supported by other investigators who have created diagnostic models for identifying patients with Crohn's disease among those with IBDs [45]. It is known that linoleic acid is used to synthesise arachidonic acid, which can be metabolised to bioactive eicosanoids such as prostaglandins, leukotrienes, thromboxanes and lipoxins that are involved in inflammation and platelet aggregation [49], including in patients with IBDs. Studies by P. Sharon et al., D.W. Hommes et al. have showed that the production of leukotrienes and prostaglandins increases in the intestinal mucosa in patients with Crohn's disease [54, 55]. The significance of the level of alpha-linolenic acid in diagnostic models is determined by the fact that it is a precursor to a number of the omega-3 PUFAs. C18:3 n-3 are metabolized into eicosapentaenoic acid (C20:5n-3) and docosahexaenoic acid (C22:6n-3) by the same desaturases that participate in the metabolism of the omega-6 PUFAs [49].

The present study has a number of certain limitations. On the one hand, a small number of observations led to the detection of only trends in the differentiation of fatty acid levels in different nosological entities of IBDs. On the other hand, a significant variation in the levels of fatty acids did not allow us to establish differentiating values for each group. Finally, the created models include a large list of fatty acids, the determination of which can be costly. Therefore, in the future, a limited number of the most diagnostically significant FAs biomarkers will be allocated, which will increase the applicability of this approach in clinical practice. In addition, monitoring patients with IBDs in dynamics will allow assessing the prognostic value of the created models.

## Conclusions

Thus, a study of fatty acid levels in groups with different nosological entities of IBDs using complex statistical analysis, including machine learning techniques, has enabled the creation of diagnostic models that differentiate Crohn's disease, ulcerative colitis and unclassified colitis in acute stage with high accuracy.

The most significant factors for distinguishing active ulcerative colitis from exacerbation of Crohn's disease were as follows: serum levels of elaidic ($p$ = 0.0006); docosatetraenoic (n-6) ($p$ = 0.004); docodienoic (n-6) ($p$ = 0.009) acids; omega-3/omega-6 ratio ($p$ = 0.02); docosapentaenoic acid (n- 3) ($p$ = 0.03); the sum of the two omega-3 PUFAs, eicosapentaenoic and docosahexaenoic acids ($p$ = 0.03); and lauric acid content of red cell membrane ($p$ = 0.04) (AUC, 0.89; sensitivity, 0.91; specificity, 0.89; diagnostic accuracy, 0.91).

To distinguish active UC from the acute stage of UCC, the following serum FAs were significant: alpha-linolenic acid, the content of saturated acids (pentadecanoic, palmitic, stearic, arachine), monounsaturated acids (palmitoleic, oleic), omega-6 (hexadecadienic, arachidonic) acids ($p$ = 0.00000011–0.03300000) (AUC, 0.995; sensitivity, 0.98; specificity, 0.96; diagnostic accuracy, 0.97).

The levels of the following FAs were the most significant for distinguishing patients with active CD from exacerbations of UCC: alpha-linolenic

acid; palmitoleic acid; oleic acid; sum of PUFAs; sum of PUFAs; stearic acid; sum of MUFAs; ratio of saturated FAs / unsaturated FAs; saturated FAs / PUFAs; linoleic acid; sum of omega-6 PUFAs; lauric acid; arachic acid ($p$ = 0.0000000017–0.0300000000) (AUC — 0.914; sensitivity — 0.90; specificity — 0.87; diagnostic accuracy — 0.91).

The proposed approach seems promising for the purposes of differential diagnosis and suggests further research with a large number of observations.

## References / Литература


1. *Головенко О.В., Хомерики С.Г., Иванова Е.В., Федоров Е.Д., Головенко А.О.* Воспалительные заболевания кишечника. Клинические, эндоскопические, морфологические аспекты диагностики. *Принципы современной терапии.* М.: Прима Принт; 2017. [*Golovenko O.V., Khomeriki S.G., Ivanova E.V., Fedorov E.D., Golovenko A.O.* Inflammatory bowel disease. Clinical, endoscopic, morphological aspects of diagnosis. *Principles of modern therapy.* Moscow: Prima Print, 2017 (In Russ.)].
2. *Ng S.C., Shi H.Y., Hamidi N., Underwood F.E., Tang W., Benchimol E.I., et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* 2017;390(10114):2769–78. DOI: 10.1016/S0140-6736(17)32448-0
3. *Maaser C., Sturm A., Vavricka S.R., Kucharzik T., Fiorino G., Annese V., et al.* European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis.* 2019;13(2):144–64. DOI: 10.1093/ecco-jcc/jjy113
4. *Colombel J.F., D'haens G., Lee W.J., Petersson J., Panaccione R.* Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. *J Crohns Colitis.* 2020;14(2):254–66. DOI: 10.1093/ecco-jcc/jjz131
5. *Gomollón F., Dignass A., Annese V., Tilg H., Assche G.V., Lindsay J.O., et al.* 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management, *Journal of Crohn's and Colitis.* 2017;11(1):3–25. DOI: 10.1093/ecco-jcc/jjw168
6. *Sturm A., Maaser C., Calabrese E., Annese V., Fiorino G., Kucharzik T., et al.* European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. *J Crohns Colitis.* 2019;13(3):273–84. DOI: 10.1093/ecco-jcc/jjy114
7. Язвенный колит: Клинические рекомендации — 2020 (22.07.20; утв. Минздравом России). *Рос. гастроэнтерол. ассоц., Ассоц. колопроктологов России.* [Ulcerative colitis: Clinical guidelines — 2020 (07/22/20; approved by the Russian Ministry of Health). *Ros. gastroenterol. assoc., assoc. Russian coloproctologists* (In Russ.)]. URL: https://legalacts.ru/doc/klinicheskie-rekomendatsii-iazvennyi-kolit-utv-minzdravom-rossii/
8. *Ивашкин В.Т., Шелыгин Ю.А., Абдулганиева Д.И., Абдулхаков Р.А., Алексеева О.П., Алексеенко С.А. и др.* Клинические рекомендации по диагностике и лечению болезни Крона у взрослых (Проект). *Колопроктология.* 2020;19(2):8–38. [*Ivashkin V.T., Shelygin Yu.A., Abdulganieva D.I., Abdulkhakov R.A., Alekseeva O.P., Alekseenko S.A., et al.* Clinical guidelines for the diagnosis and treatment of Crohn's disease in adults ( Project). *Coloproctology.* 2020;19(2):8–38 (In Russ.)]. DOI: 10.33878/2073-7556-2020-19-2-8-38
9. *Nuij V.J., Zelinkova Z., Rijk M.C., Beukers R., Ouwendijk R.J., Quispel R., et al.* Phenotype of inflammatory bowel disease at diagnosis in the Netherlands: a population-based inception cohort study (the Delta Cohort). *Inflamm Bowel Dis* 2013;19:2215–22. DOI: 10.1097/MIB.0b013e3182961626
10. *Burisch J., Pedersen N., Čuković-Čavka S., Brinar M., Kaimakliotis I., Duricova D., et al.* East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. Gut. 2014;63:588–97. DOI: 10.1136/gutjnl-2013-304636
11. *Abraham B.P., Mehta S., El-Serag H.B.* Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol.* 2012;46(7):581–9. DOI: 10.1097/MCG.0b013e318247c32f
12. *Henriksen M., Jahnsen J., Lygren I., Sauar J., Schulz T., Stray N., et al.* Change of diagnosis during the first five years after onset of inflammatory bowel disease: results of a prospective follow-up study (the IBSEN Study). *Scand J Gastroenterol.* 2006;41(9):1037–43. DOI: 10.1080/00365520600554527.
13. *Melmed G.Y., Elashoff R., Chen G.C., Nastaskin I., Papadakis K.A., Vasiliauskas E.A., et al.* Predicting a change in diagnosis from ulcerative colitis to Crohn's disease: a nested, case-control study. *Clin Gastroenterol Hepatol.* 2007;5(5):602–8; quiz 525. DOI: 10.1016/j.cgh.2007.02.015
14. *Tontini G.E., Vecchi M., Pastorelli L., Neurath M.F., Neumann H.* Differential diagnosis in inflammatory bowel disease colitis: state of the art and future perspectives. *World J Gastroenterol.* 2015;21(1):21–46. DOI: 10.3748/wjg.v21.i1.21
15. *Odze R.* Diagnostic problems and advances in inflammatory bowel disease. *Mod Pathol.* 2003;16(4):347–58. DOI: 10.1097/01.MP.0000064746.82024.D1
16. *Bauset C., Gisbert-Ferrándiz L., Cosín-Roger J.* Metabolomics as a Promising Resource Identifying Potential Biomarkers for Inflammatory Bowel Disease. *J Clin Med.* 2021;10(4):622. DOI: 10.3390/jcm10040622
17. *Negreanu L., Voiosu T., State M., Voiosu A., Bengus A., Mateescu B.R.* Endoscopy in inflammatory bowel disease: from guidelines to real life. *Therap Adv Gastroenterol.* 2019;12:1756284819865153. DOI: 10.1177/1756284819865153
18. *Panes J., Jairath V., Levesque B.G.* Advances in Use of Endoscopy, Radiology, and Biomarkers to Monitor Inflammatory Bowel Diseases. *Gastroenterology.* 2017;152(2):362–73.e3. DOI: 10.1053/j.gastro.2016.10.005
19. *Lai Y., Xue J., Liu C.W., Gao B., Chi L., Tu P., et al.* Serum Metabolomics Identifies Altered Bioenergetics, Signaling Cascades in Parallel with Exposome Markers in Crohn's Disease. *Molecules.* 2019;24(3):449. DOI: 10.3390/molecules24030449
20. *Seyedian S.S., Nokhostin F., Malamir M.D.* A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *J Med Life.* 2019;12(2):113–22. DOI: 10.25122/jml-2018-0075
21. *State M., Negreanu L., Voiosu T., Voiosu A., Balanescu P., Mateescu R.B.* Surrogate markers of mucosal healing in inflammatory bowel disease: A systematic review. *World J Gastroenterol.* 2021;27(16):1828–40. DOI: 10.3748/wjg.v27.i16.1828
22. *Chen P., Zhou G., Lin J., Li L., Zeng Z., Chen M., et al.* Serum Biomarkers for Inflammatory Bowel Disease. *Front Med (Lausanne).* 2020;7:123. DOI: 10.3389/fmed.2020.00123
23. *Derbyshire E.* Brain Health across the Lifespan: A Systematic Review on the Role of Omega-3 Fatty Acid Supplements. *Nutrients.* 2018;10(8):1094. DOI: 10.3390/nu10081094
24. *Djuricic I., Calder P.C.* Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. *Nutrients.* 2021;13(7):2421. DOI: 10.3390/nu13072421

25. *Michalak A., Mosińska P., Fichna J.* Polyunsaturated Fatty Acids and Their Derivatives: Therapeutic Value for Inflammatory, Functional Gastrointestinal Disorders, and Colorectal Cancer. *Front Pharmacol.* 2016;7:459. DOI: 10.3389/fphar.2016.00459
26. *Scaioli E., Liverani E., Belluzzi A.* The Imbalance between n-6/n-3 Polyunsaturated Fatty Acids and Inflammatory Bowel Disease: A Comprehensive Review and Future Therapeutic Perspectives. *Int J Mol Sci.* 2017;18(12):2619. DOI: 10.3390/ijms18122619
27. *Marton L.T., Goulart R.A., Carvalho A.C.A., Barbalho S.M.* Omega Fatty Acids and Inflammatory Bowel Diseases: An Overview. *Int J Mol Sci.* 2019;20(19):4851. DOI: 10.3390/ijms20194851
28. *Tomaiuolo G., Lanotte L., D'Apolito R., Cassinese A., Guido S.* Microconfined flow behavior of red blood cells. *Med Eng Phys.* 2016;38(1):11–6. DOI: 10.1016/j.medengphy.2015.05.007
29. *Durkin L.A., Childs C.E., Calder P.C.* Omega-3 Polyunsaturated Fatty Acids and the Intestinal Epithelium-A Review. *Foods.* 2021;10(1):199. DOI: 10.3390/foods10010199
30. *Masoodi M., Pearl D.S., Eiden M., Shute J.K., Brown J.F., Calder P.C., et al.* Altered colonic mucosal Polyunsaturated Fatty Acid (PUFA) derived lipid mediators in ulcerative colitis: new insight into relationship with disease activity and pathophysiology. *PLoS One.* 2013;8(10):e76532. DOI: 10.1371/journal.pone.0076532
31. *Satsangi J., Silverberg M.S., Vermeire S., Colombel J.F.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut.* 2006;55(6):749–53. DOI: 10.1136/gut.2005.082909
32. *Silverberg M.S., Satsangi J., Ahmad T., Arnott I.D., Bernstein C.N., Brant S.R., et al.* Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J *Gastroenterol.* 2005;19 Suppl A:5A–36A. DOI: 10.1155/2005/269076
33. *Кручинина М.В., Кручинин В.Н., Прудникова Я.И., Громов А.А., Шашков М.В., Соколова А.С.* Исследование уровня жирных кислот мембран эритроцитов и сыворотки крови у пациентов с колоректальным раком г. Новосибирска. *Успехи молекулярной онкологии.* 2018;5(2):50–61. [*Kruchinina M.V., Kruchinin V.N., Prudnikova Y.I., Gromov A.A., Shashkov M.V., Sokolova A.S.* Study of the level of fatty acids in erythrocyte membrane and serum of patients with colorectal cancer in Novosibirsk. *Advances in Molecular Oncology.* 2018;5(2):50–61 (In Russ.)]. DOI: 10.17650/2313-805X-2018-5-2-50-61
34. *Breiman, L.* Random Forests. *Machine Learning.* 2001;45:5–32. DOI: 10.1023/A:1010933404324
35. *De Preter V.* Metabolomics in the Clinical Diagnosis of Inflammatory Bowel Disease. *Dig Dis.* 2015;33 Suppl 1:2–10. DOI: 10.1159/000437033
36. *Nicholson J.K., Lindon J.C.* Systems biology: Metabonomics. *Nature.* 2008;455(7216):1054–6. DOI: 10.1038/4551054a
37. *Williams H.R., Willsmore J.D., Cox I.J., Walker D.G., Cobbold J.F., Taylor-Robinson S.D., et al.* Serum metabolic profiling in inflammatory bowel disease. *Dig Dis Sci.* 2012;57(8):2157–65. DOI: 10.1007/s10620-012-2127-2
38. *Hisamatsu T., Okamoto S., Hashimoto M., Muramatsu T., Andou A., Uo M., et al.* Novel, objective, multivariate biomarkers composed of plasma amino acid profiles for the diagnosis and assessment of inflammatory bowel disease. *PLoS One.* 2012;7(1):e31131. DOI: 10.1371/journal.pone.0031131
39. *Ooi M., Nishiumi S., Yoshie T., Shiomi Y., Kohashi M., Fukunaga K., et al.* GC/MS-based profiling of amino acids and TCA cycle-related molecules in ulcerative colitis. *Inflamm Res.* 2011;60(9):831–40. DOI: 10.1007/s00011-011-0340-7
40. *Scoville E.A., Allaman M.M., Brown C.T., Motley A.K., Horst S.N., Williams C.S., et al.* Alterations in Lipid, Amino Acid, and Energy Metabolism Distinguish Crohn's Disease from Ulcerative Colitis and Control Subjects by Serum Metabolomic Profiling. *Metabolomics.* 2018;14(1):17. DOI: 10.1007/s11306-017-1311-y
41. *Kolho K.L., Pessia A., Jaakkola T., de Vos W.M., Velagapudi V.* Faecal and Serum Metabolomics in Paediatric Inflammatory Bowel Disease. *J Crohns Colitis.* 2017;11(3):321–34. DOI: 10.1093/ecco-jcc/jjw158
42. *Кручинина М.В., Азгалдян А.В., Светлова И.О., Шашков М.В., Соколова А.С., Кручинин В.Н.* Особенности состава жирных кислот сыворотки крови и мембран эритроцитов у пациентов с воспалительными заболеваниями кишечника (пилотное исследование). *Современные проблемы науки и образования.* 2019;3. URL: https://science-education.ru/ru/article/view?id=28868 (дата обращения: 20.02.2022). [*Kruchinina M.V., Azgaldyan A.V., Svetlova I.O., Shashkov M.V., Sokolova A.S., Kruchinin V.N.* Features of the composition of fatty acids in blood serum and erythrocyte membranes in patients with inflammatory bowel diseases (pilot study). *Modern problems of science and education*. 2019;3. URL: https://science-education.ru/ru/article/view?id=28868 (date of access: 20.02.2022) (In Russ.)]. DOI: 10.17513/spno.28868
43. *Uchiyama K., Nakamura M., Odahara S., Koido S., Katahira K., Shiraishi H., et al.* N-3 polyunsaturated fatty acid diet therapy for patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2010;16(10):1696–707. DOI: 10.1002/ibd.21251
44. *Marion-Letellier R., Savoye G., Beck P.L., Panaccione R., Ghosh S.* Polyunsaturated fatty acids in inflammatory bowel diseases: a reappraisal of effects and therapeutic approaches. *Inflamm Bowel Dis.* 2013;19(3):650–61. DOI: 10.1097/MIB.0b013e3182810122
45. *Ito Z., Uchiyama K., Odahara S., Takami S., Saito K., Kobayashi H., et al.* Fatty Acids as Useful Serological Markers for Crohn's Disease. *Dig Dis.* 2018;36(3):209–17. DOI: 10.1159/000485096
46. *Friedman A.N., Yu Z., Tabbey R., Denski C., Tamez H., Wenger J., et al.* Low blood levels of long-chain n-3 polyunsaturated fatty acids in US hemodialysis patients: clinical implications. *Am J Nephrol.* 2012;36(5):451–8. DOI: 10.1159/000343741
47. *Ge Sh., Lu H., Li Q., Logan H. L., Dodd V., Bian J., et al.* Classification Tree Analysis of Factors Associated with Oral Cancer Exam. *American Journal of Health Behavior*. 2019;43:635–47. DOI: 10.5993/AJHB.43.3.16
48. *Shores D.R., Binion D.G., Freeman B.A., Baker P.R.* New insights into the role of fatty acids in the pathogenesis and resolution of inflammatory bowel disease. *Inflamm Bowel Dis*. 2011 Oct;17(10):2192–204. DOI: 10.1002/ibd.21560
49. *Таганович А.Д., Олецкий Э.И., Котович И.Л.* Патологическая биохимия / Под общ. ред. А.Д. Тагановича. М.: *БИНОМ*, 2013 [*Taganovich A.D., Oletsky E.I., Kotovich I.L.* Pathological biochemistry / Under total ed. A.D. Taganovich. Moscow: *BINOM Publ.*, 2013 (In Russ.)].
50. *Seimon T.A., Nadolski M.J., Liao X., Magallon J., Nguyen M., Feric N.T., et al.* Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. *Cell Metab.* 2010;12(5):467–82. DOI: 10.1016/j.cmet.2010.09.010
51. *Saraswathi V., Hasty A.H.* Inhibition of long-chain acyl coenzyme A synthetases during fatty acid loading induces lipotoxicity in macrophages. *Arterioscler Thromb Vasc Biol.* 2009;29(11):1937–43. DOI: 10.1161/ATVBAHA.109.195362
52. *Wiese D.M., Horst S.N., Brown C.T., Allaman M.M., Hodges M.E., Slaughter J.C., et al.* Serum Fatty Acids Are Correlated with Inflammatory Cytokines in Ulcerative Colitis. *PLoS One.* 2016;11(5):e0156387. DOI: 10.1371/journal.pone.0156387
53. *Scoville E., Allaman M., Adams D., Motley A., Peyton S., Ferguson S., et al.* Serum Polyunsaturated Fat-

ty Acids Correlate with Serum Cytokines and Clinical Disease Activity in Crohn's Disease. *Scientific Reports*. 2019;9:2882. DOI: 10.1038/s41598-019-39232-z
54. *Sharon P., Stenson W.F.* Enhanced synthesis of leukotriene B4 by colonic mucosa in inflammatory bowel disease. *Gastroenterology.* 1984 Mar;86(3):453–60.
55. *Hommes D.W., Meenan J., de Haas M., ten Kate F.J., von dem Borne A.E., Tytgat G.N., et al.* Soluble Fc gamma receptor III (CD 16) and eicosanoid concentrations in gut lavage fluid from patients with inflammatory bowel disease: reflection of mucosal inflammation. *Gut*. 1996;38(4):564–7. DOI: 10.1136/gut.38.4.564

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