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IMPACT OF COVID-19 ON INFLAMMATORY BOWEL DISEASE: COURSE AND OUTCOME

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Abstract

Introduction. Coronavirus infection is an acute viral disease with a primary lesion of the upper respiratory tract, caused by an RNA-virus of the Betacoronavirus genus of the Coronaviridae family. The course of a viral infection varies from asymptomatic to a wide range of clinical manifestations, including fever, chills, gastrointestinal manifestations, pneumonia, respiratory distress, and death.

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic immune-mediated diseases with intestinal and systemic symptoms, which are based on an impairment of the intestinal microbiota and dysregulation of the immune system in genetically predisposed individuals. In the Kazakh population, risk factors also include irregular food intake (p=0.043; OR=3.61 [95% CI: 1.04–12.51]), consumption of fish and seafood (p=0.000; OR= 15.77 [95% CI: 4.56-54.59]), consumption of frozen processed foods (p = 0.018; OR = 4.62 [95% CI: 1.3-16.4]), diet based on meat dishes (p=0.029; OR=3.2 [95% CI: 1.13-9.2]), use of NSAIDs other than aspirin (p=0.031; OR=3.79 [1.13-12.69]) and smoking (p=0.008; OR=4.93 [95% CI: 1.52-15.98]) [26].

The suppression of the immune response is associated with the risk of infection with viral or bacterial pathogens, including potentially the SARS-CoV-2 virus. On the other hand, SARS-CoV-2 infection as a potential trigger factor for de novo occurrence of inflammatory bowel disease is currently being discussed [22, 25].

The aim of this study was to assess the characteristics of the course of COVID-19 during the treatment of inflammatory bowel diseases (IBD), risk factors and outcomes of COVID-19, as well as the activity of IBD before and after a coronavirus infection.

Materials and methods. A longitudinal descriptive study included 158 patients with IBD who applied on an outpatient basis (including via remote consultation) or inpatient with SARS-Cov2 or COVID-19 infection in the academic centers of Almaty (Kazakhstan) n=54 and St. Petersburg (Russia), n= 104. The observation period was from May 2020 to May 2022.

The median and interquartile range were used to describe quantitative data (age), and absolute frequencies and percentages were used for qualitative data. The Mann-Whitney U-test was used for intergroup comparison of quantitative data (age), for the remaining indicators, the likelihood ratio test (Likehood ratio test), and in the case of 2X2 tables, Fisher's exact test.

Results. There was no association between IBD type/activity or drugs taken and the severity of COVID-19. However, the severity of COVID-19 affected the activity of IBD. We`ve identified the same risk factors for the development of a more severe course of COVID-19 were as in the world literature: cardiovascular pathology, arterial hypertension and chronic liver pathology.

Conclusion. Thus, inflammatory bowel disease and current therapy do not affect the risk of SARS-Cov-2 infection and/or the severity of COVID-19, while infection associated with severe COVID-19 affects the activity or outcomes of IBD.

Keywords: *Inflammatory bowel disease, COVID-19, SARS-CoV-2, ulcerative colitis, Crohn's disease.*

Резюме

ВЛИЯНИЕ COVID-19 НА ВОСПАЛИТЕЛЬНЫЕ ЗАБОЛЕВАНИЯ КИШЕЧНИКА: ТЕЧЕНИЕ И ИСХОДЫ

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Актуальность. Коронавирусная инфекция – острое вирусное заболевание с преимущественным поражением верхних дыхательных путей, вызываемое РНК-геномным вирусом рода Betacoronavirus семейства Coronaviridae. Заражение вирусом варьируется от бессимптомного до широкого спектра клинических проявлений, включая лихорадку, озноб, желудочно-кишечные проявления, пневмонию, респираторный дистресс и смерть.

Язвенный колит (ЯК) и болезнь Крона (БК) – хронические иммуноопосредованные заболевания с кишечной и системной симптоматикой, в основе которых лежат нарушение микробиоты кишечника и дисрегуляция иммунной системы у генетически-предрасположенных лиц. У лиц казахской популяции к факторам риска также можно отнести нерегулярный прием пищи (p=0,043; ОШ=3,61 [95% ДИ: 1,04-12,51]), потребление рыбы и морских продуктов (p=0,000; ОШ=15,77 [95% ДИ: 4,56-54,59]), потребление замороженных полуфабрикатов (p=0,018; ОШ=4,62 [95% ДИ: 1,3-16,4]), питание, основанное на мясных блюдах (p=0,029; ОШ=3,2 [95%ДИ: 1,13-9,2]), применение НПВС, кроме аспирина (p=0,031; ОШ=3,79 [1,13-12,69]) и курение (p=0,008; ОШ=4,93 [95% ДИ: 1,52-15,98]) [26].

Подавление иммунного ответа ассоциировано с риском инфицирования вирусными или бактериальными патогенами, в том числе, потенциально вирусом SARS-CoV-2. С другой стороны, в настоящее время обсуждается SARS-Cov2 в качестве триггера de-novo ВЗК случаев [22, 25].

Цель проведенного исследования: оценить особенности течения COVID-19 на фоне терапии воспалительных заболеваний кишечника, факторы риска и исходы COVID-19, а также активность ВЗК до и после перенесенной КВИ.

Материалы и методы. Продольное описательное исследование включало 158 пациентов с ВЗК, обратившихся амбулаторно (в том числе посредством дистанционной консультации) или стационарно с инфекцией SARS-Cov2 или COVID-19 в академических центрах Алматы (Казахстан), n=54 и Санкт-Петербурга (Россия), n=104. Период наблюдения был с мая 2020 по май 2022.

Для описания количественных данных (возраст) были использованы медиана и межквартильный размах, для качественных данных - абсолютные частоты и проценты. Для межгруппового сравнения количественных данных (возраст) применялся U-критерий Манна-Уитни, для остальных показателей тест отношения правдоподобия (Likehood ratio test), а в случае таблиц 2X2 Точный тест Фишера.

Результаты. Не было выявлено связи между типом/активностью ВЗК или принимаемыми препаратами и тяжестью течения COVID-19. Однако, тяжесть течения COVID-19 влияла на активность ВЗК. Выявлены те же факторы риска развития более тяжелого течения COVID-19, что и в мировой литературе: сердечно-сосудистая патология, артериальная гипертензия и хроническая патология печени.

Заключение. Таким образом, воспалительное заболевание кишечника и текущая терапия не влияют на риск заражения SARS-Cov-2 и/или тяжесть течения COVID-19, в то же время, инфекция, ассоциированная с тяжелым течением COVID-19 влияет на активность или исходы ВЗК.

Ключевые слова: *воспалительные заболевания кишечника, COVID-19, SARS-CoV-2, язвенный колит, болезнь Крона.*

Түйіндеме

COVID-19-ның ІШЕКТІҢ ҚАБЫНУ АУРУЛАРЫНА ӘСЕРІ: АУРУДЫҢ АҒЫМЫ ЖӘНЕ НӘТИЖЕЛЕРІ

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Өзектілігі. Коронавирустық инфекция – Coronaviridae тұқымдасының Betacoronaviridae тектес РНҚ геномдық вирусынан туындайтын жоғарғы тыныс алу жолдарының басым зақынданyы бар жедел вирустық ауру. Вирусты жұқтыру симптомсыз түрінен қызба, қалтырау, асқазан-ішек жолдарының көріністерімен, пневмония, респираторлық дистресс және өлім сияқты кең спектрлі клиникалық көрініске дейін өзгереді.

Жаралы колит (ЖК) және Крон ауруы (КА) – ішек микробиотының бұзылуымен және генетикалық бейімділігі бар адамдардың иммундық жүйесінің дисрегуляциясына негізделген ішектік және жүйелік симптомдары бар созылмалы иммуносуперессорлық ауру. Ұлты қазақ тұлғаларда қауіп факторларына тамақты тұрақты емес тұтыну (p=0,043; OR=3,61 [95% CI: 1,04–12,51]), балық пен теңіз өнімдерін тұтыну (p=0,000; OR= 15,77 [95% CI: 4,56-54,59]), мұздатылған өңделген тағамдарды тұтыну (p = 0,018; OR = 4,62 [95% CI: 1,3-16,4]), ет тағамдарына негізделіп тамақтану (p=0,029; OR=3,2 [95% CI: 1,13-9,2]]), аспирин (p=0,031; OR=3,79 [1,13-12,69]) және темекі шегуден басқа (p=0,008; OR=4,93 [95% CI: 1,52-15,98]) ҚҚСД (қабынуға қарсы стероидтық емес дәрілік заттар) қолдануды жатқызуға болады [26].

Иммундық реакцияны басу вирустық немесе бактериялық қоздырғыштармен, оның ішінде ықтимал SARS-CoV-2 вирусымен жұқтыру қаупімен байланысты. Екінші жағынан, қазіргі уақытта SARS-Cov 2 de-novo IBD жағдайларының триггері ретінде талқылануда [22, 25].

Зерттеуді жүргізудің мақсаты: ішектің қабыну ауруларын емдеу көрінісінде COVID-19 ағымының ерекшеліктерін, COVID-19 қауіп факторлары мен нәтижелерін, сондай-ақ сондай-ақ коронавирустық инфекцияға дейін және одан кейінгі ІҚА белсенділігін бағалау.

Материалдар мен әдіс-тәсілдер. Бойлық сипаттамалық зерттеуге Алматы (Қазақстан), N=54 және Санкт-Петербург (Ресей), N= 104 академиялық орталықтарында амбулаториялық (оның ішінде қашықтықтан консультация беру арқылы) немесе SARS-Cov2 немесе COVID-19 инфекциясымен стационарда жүгінген ІҚА-мен ауыратын 158 пациент кіргізілді. Бақыланатын кезеңі 2020 жылдың мамыр айынан 2022 жылдың мамыр айына дейінгі уақытты қамтыды.

Сандық деректерді (жасты) сипаттау үшін медианалық және квартильді ауқым пайдаланылды, сапалы деректер үшін - абсолютті жиіліктер мен пайыздар қолданылды. Сандық деректерді (жасты) топаралық салыстыру үшін Манн-Уитни U-критерийі, қалған көрсеткіштер үшін ықтималдылық қатынасы тесті (Likehood ratio test), ал 2x2 кестелер жағдайында Фишердің дәл тесті қолданылды.

Нәтижелер. ІҚА түрі/белсенділігі немесе қабылданған препараттар мен COVID-19 ағымының ауырлығы арасында ешқандай байланыс анықталмады. Дегенмен, COVID-19 ауырлығы ІҚА белсенділігіне әсер етті. Әлемдік әдебиеттердегідей, COVID-19 неғұрлым ауыр ағымының даму қауіп факторлары анықталды: жүрек-қан тамыр патологиясы, артериялық гипертензия және бауырдың созылмалы ауруы.

Қорытынды. Осылайша, ішектің қабыну ауруы және ағымдағы терапия SARS-Cov-2 инфекциясын жұқтыру қаупіне және/немесе COVID-19 ағымының ауырлығына әсер етпейді, ал сонымен қатар COVID-19 ауыр ағымысен байланысты инфекция ІҚА белсенділігіне немесе нәтижелеріне әсер етеді.

Түйінді сөздер: Ішектің қабыну ауырлары, COVID-19, SARS-CoV-2, ойық жаралы колит, Крон ауруы.

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Танабаева А.С., Губонина И.В., Гриневич В.Б., Колодин Т.В., Жумадилова З.К., Жанабаева А., Агзамова З.Х., Амирова А.М., Уалиева А.Е., Нерсесов А.В., Кайбуллаева Д.А. Влияние COVID-19 на воспалительные заболевания кишечника: течение и исходы // Наука и Здравоохранение. 2022. 4(Т.24). С. 12-18. *doi 10.34689/SH.2022.24.4.002*

Танабаева А.С., Губонина И.В., Гриневич В.Б., Колодин Т.В., Жумадилова З.К., Жанабаева А., Агзамова З.Х., Амирова А.М., Уалиева А.Е., Нерсесов А.В., Кайбуллаева Д.А. COVID-19-ның ішектің қабыну ауруларына әсері: аурудың ағымы және нәтижелері // Ғылым және Денсаулық сақтау. 2022. 4 (Т.24). Б. 12-18. *doi 10.34689/SH.2022.24.4.002*

Introduction

Coronavirus infection is an acute viral disease with a primary lesion of the upper respiratory tract, caused by an RNA-virus of the Betacoronavirus genus of the Coronaviridae family. To date, the most commonly identified risk factors for severe COVID-19 are age, cardiovascular disease, chronic respiratory disease, obesity, and diabetes [2].

The course of a viral infection varies from asymptomatic to a wide range of clinical manifestations, including fever, chills, gastrointestinal manifestations, pneumonia, respiratory distress, and death. As of July 2021, there have been over 190 million cases and over 4 million deaths worldwide [7].

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic immune-mediated diseases with intestinal and systemic symptoms, which are based on an impairment of the intestinal microbiota and dysregulation of the immune system in genetically predisposed individuals [20]. Over the past decade, IBD has become a global public health problem. Increasing incidence in populations with a previously lower prevalence of IBD confirms the influence of the environment, both on the development of Crohn's disease and on ulcerative colitis [22]. The goal of therapy for inflammatory bowel disease (IBD) is to control immune inflammation, which is achieved by the appointment of hormonal, immunosuppressive and / or biological therapy [3].

Over the past two years, the global medical community has been concerned about two questions. First: are patients with IBD at increased risk of contracting Covid-19? Second: can immunomodulators or biologics, which are used to treat IBD, increase the risk of developing severe forms of Covid-19? [17].

Since the suppression of the immune response is associated with the risk of infection with viral or bacterial pathogens [1,13,15,16,23], including potentially the SARS-CoV-2 virus, the risk of infection in patients with IBD, the course of infection against the background of this pathology, as well as outcomes for IBD were analyzed from the beginning of the COVID-19 pandemic [14]. To enter the human body, the SARS-Cov-2 virus uses its surface glycoprotein (S-protein), by which the virus binds to angiotensin-converting enzyme-2 (ACE-2), an exopeptidase that catalyzes the conversion of angiotensin I to angiotensin 1-9 and angiotensin II to angiotensin 1-7 [8,12]. ACE-2 is not organ-specific and is expressed in many tissues, including the terminal ileum and colon, the sites where inflammation is most commonly found in IBD patients [23]. Immunohistochemical studies have shown that the expression of ACE-2 in the terminal small intestine and in the colon in samples from patients with IBD is higher compared to healthy people [9-11].

To date, the actual infection risk or developing COVID-19 in these at-risk patients with IBD or in patients receiving immunosuppressive treatment for IBD is not clear. In addition, it is not known whether any dose adjustments can be made to reduce the risk of CVI infection without increasing disease activity. Throughout the COVID-19 pandemic, the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has provided guidance on the management of IBD, such as the encouragement to continue biologic therapies and only temporarily holding them when infected [24].

However, recent studies still show the possible impact of the virus on autoimmunity and the likelihood of developing new cases of IBD after infection [25].

This publication presents the results of a retrospective multicenter follow-up of patients with IBD during COVID-19.

The aim of this study was to assess the characteristics of the course of COVID-19 during the treatment of inflammatory bowel diseases (IBD), risk factors and outcomes of COVID-19, as well as the activity of IBD before and after a coronavirus infection.

Materials and methods. This is a longitudinal, descriptive, multicenter study. Data were collected on the basis of two academic care centers – Research Institute of cardiology and Internal diseases (inpatients) and Center of gastroenterology and hepatology (outpatient clinic) in Almaty (Kazakhstan), a total of 618 patients with IBD are observed and in the Scientific and Practical Center for IBD Military-medical Academy St. Petersburg (Russia), a total of 269 patients with IBD.

Patient identification. All incidental visits of patients with IBD ≥ 18 years of age as outpatients (including through online counseling) or inpatients with a history of SARS-CoV-2 and/or COVID-19 infection were considered cases for observation and were included in the study. Diagnosis of COVID-19 was based on positive SARS-CoV-2 polymerase chain reaction (PCR) and/or COVID-19 (CO-RADS) findings on chest computed tomography [6].

Data collection. We analyzed age, gender, nationality, IBD diagnosis, IBD activity, IBD therapy at the time of COVID-19 diagnosis, concomitant diagnoses.

Furthermore, we analyzed the following variables related to COVID-19: date of diagnosis, clinical symptoms and signs, SARS-CoV-2 PCR result, CO-RADS chest computed tomography result, and medication. In addition, we collected COVID-19 outcomes including death, duration of hospitalization in intensive care unit (ICU), and ICU treatment, including mechanical ventilation, renal replacement therapy, and extracorporeal membrane oxygenation, and vaccination status against COVID-19. We used an international database «Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease» (SECURE-IBD) to create a local database [27]. At the time of writing this article,

the international database includes data from more than 7,000 patients with IBD from more than 70 countries. QCovid® risk calculator was used to calculated the risk of death and hospitalization [5].

Statistical Methods. The median and interquartile range were used to describe quantitative data (age), and absolute frequencies and percentages were used for qualitative data. For intergroup comparison of quantitative data (age), the Mann-Whitney U-test was used, for the remaining indicators, the likelihood ratio test (Likehood ratio test), and in the case of 2X2 tables, Fisher's exact test. The value p<0.05 was chosen as a statistically significant level.

Ethical approval. The ethical approval of the Central Commission for Bioethics was received on June 23, 2021 (Protocol No. 9).

Results.

In total, 158 patients with IBD who underwent COVID-19 were included in the observation, 54 patients were from Almaty, Kazakhstan and 104 patients were from Saint Petersburg, Russia; Figure 1 shows the severity distribution of COVID-19 by nationality. The mean age was 35 years (p=0.025).

Mild course was more often observed in men - 65.6% (n-86), while moderate and severe occurred with approximately the same frequency: 53.8% (n = 14), men and 46.2% (n=12), women. The majority of patients with IBD experienced mild COVID-19: 73 patients with UC and 57 patients with CD.

Impact of COVID-19 on the course of IBD. Analysis of the results of the influence of infection on the course of IBD showed that after suffering a severe pathology due to COVID-19, there was a decrease in cases of minimal activity and an increase in the frequency of high activity of IBD (p=0.001) in comparison with the activity of intestinal pathology at the time of infection (p=0.064) (Likelihood ratio).

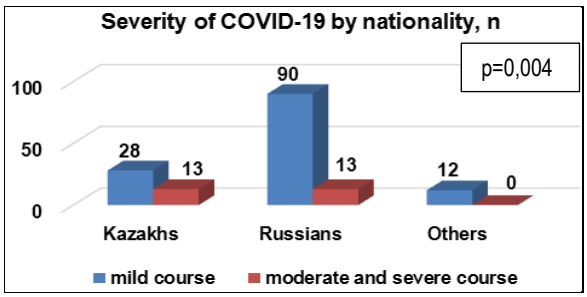

Figure 1. COVID-19 severity by nationality.

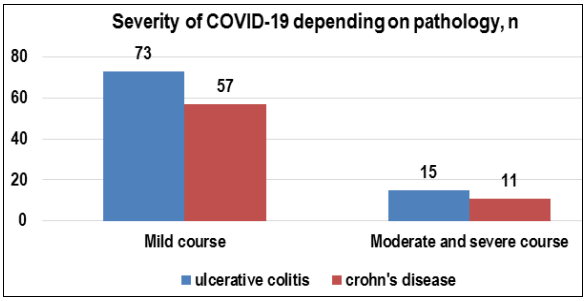

Figure 2. Distribution by severity of COVID-19 depending on the pathology.

Table 1. **IBD activity before and after SARS-Cov-2 or COVID-19 infection.**

IBD activity	Severity of Covid					
		Mild course		Moderate and severe course		p
At the time of Covid 19	Remission	62	47,3%	5	19,2%	0,064
	Mild	30	22,9%	8	30,8%	
	Moderate	30	22,9%	10	38,5%	
	Severe	9	6,9%	3	11,5%	
After Covid- 19 infection	Remission	69	52,7%	5	19,2%	0,001
	Mild	29	22,1%	6	23,1%	
	Moderate	24	18,3%	6	23,1%	
	Severe	9	6,9%	9	34,6%	

The vast majority of patients were on 5-aminosalicylate therapy (56.2% in mild coronavirus infection (CVI) and 80.8% in severe), steroid therapy was received by 16.5% of IBD patients with mild CVI and a third of patients with severe CVI. A total of 37 people were on biological therapy, of which 22 received anti-TNF agents against the background of a mild course of COVID-19 and 4 against the background of a moderate and severe course of infection. 7 mild and 3 moderate to severe patients were on anti-integrin therapy, 1 patient was on ustekinumab, and 2 patients were not on any IBD therapy.

Among the comorbidities, the most significant association for the more severe course of COVID-19 was with cardiovascular pathologies (p=0.028), arterial hypertension (p=0.006) and chronic liver pathology (primary sclerosing cholangitis, non-alcoholic fatty liver disease, liver cirrhosis, p=0.020) (Figure 3). Further, analyzing the complications of COVID-19, it should be noted that, in general, complications are typical for a more serious course (p=0.008), while the most significant in moderate and severe cases were acute respiratory distress syndrome (p=0.015), pneumonia (p=0.026) or other serious complications (p=0.004).

Antibacterial therapy was prescribed for mild COVID-19 in 13% and 46.2% (p<0.001). 4.6% of patients with mild and 8.0% of patients with severe disease were vaccinated at the time of infection with COVID-19.

We calculated the risk of death and hospitalization according to the QCovid® risk calculator [5] (Table 2). QCovid was developed as a model to estimate a person's risk of being hospitalized or dying due to catching coronavirus. Indicators such as the presence of vaccination against COVID-19, age, gender, ethnicity, the presence of comorbidities such as diabetes mellitus, chronic kidney disease, sickle cell anemia, severe combined immunodeficiency syndrome, neurological problems, pathology of the pulmonary and cardiovascular systems, as well as the presence of autoimmune diseases and cancer treatments and immunosuppressants were used to calculate the risks of death and hospitalization during CVI.

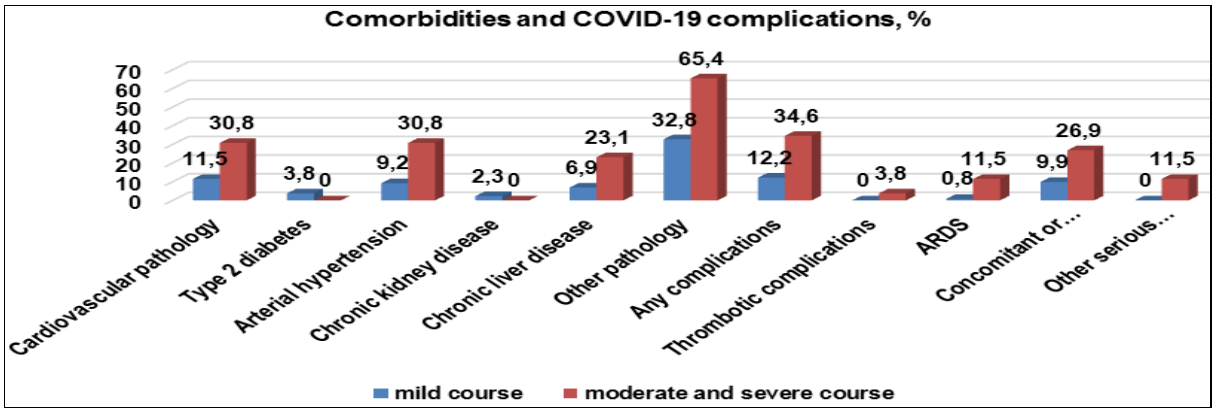

Figure 3. IBD comorbidities and complications of COVID-19.

Table 2. **COVID-19 associated risks.**

Index	Mild course		Moderate and severe course		p
	Me	IQR	Me	IQR	
Relative risk of death	1,3	1,0	2,1	1,5	0,002
Hospitalization risk	1,3	0,6	2,5	2,0	0,000
Absolute risk of death	28,0	34,0	45,5	35,3	0,009

Discussion.

A longitudinal descriptive study included 158 patients with IBD who applied on an outpatient basis (including via remote consultation) or inpatient with SARS-Cov2 or COVID-19 infection in the academic centers of Almaty (Kazakhstan), n=54 and St. Petersburg (Russia), n=104.

The outcome of hospitalization or mortality after COVID-19 in patients with IBD is similar to patients without IBD. A mild course of the disease was more often observed in men - 65.6% (n-86), while moderate and severe cases occurred with approximately the same frequency: 53.8% (n = 14), men and 46.2% (n = 12), women. The nosological unit of IBD did not affect the severity of COVID-19: 73 patients with UC and 57 patients with CD. At the same time, the activity of IBD was not affected by infection with the SARS-Cov-2 virus or the severity of the course of COVID-19,

Risk factors (comorbidities) for the development of a more severe course of COVID-19 were the following: cardiovascular pathology (p=0.028), arterial hypertension (p=0.006) and chronic liver pathology (primary sclerosing cholangitis, non-alcoholic fatty liver disease, liver cirrhosis, p=0.020). In addition, negative outcomes were associated with older age and male gender, similar risk factors in the general population, while IBD patients with COVID-19 receiving long-term biologics or non-steroidal immunomodulatory therapy were not at higher risk of adverse COVID-19 outcomes [18,21], which is consistent with the world literature data [4,17]. It was also quite natural to develop complications in severe cases (p=0.008), the most significant in moderate and severe cases were ARDS (p=0.015), pneumonia (p=0.026) or other serious complications (p=0.004).

According to the QCovid® risk calculator, the risk of death and hospitalization was 1,66 and 1,58 respectively., Cases of IBD de novo were noted in 11% (n=18) of patients and only in 3 (16%) patients out of 18 IBD activity became higher after CVI.

Overall, the results of our study shows that commonly used drugs for the treatment of IBD, including biologics and 5-aminosalicylates, are not associated with severe COVID-19 outcomes, and some drugs may even have a protective effect, which correlates with international data [26].

However, on the other hand, when analyzing the results of the influence of infection on the course of IBD, we found a change in the nature of the course of autoimmune pathology after suffering COVID-19. Thus, there was a decrease in the minimum activity and an increase in the frequency of high activity of IBD (p = 0.001) in comparison with the activity of the inflammatory process at the time of infection (p = 0.064), see Table 1. Undoubtedly, it is necessary to take into account the differences in the Russian cohort (observation of employees with IBD in Military Medical Academy) and persons with IBD who were under observation in the tertiary centers of Kazakhstan. One of the important reasons for the activation of autoimmune pathology can be called interruptions in therapy (immunosuppressive and / or biological), which was associated with impaired access to medical centers and adequate medical care during the lockdown. Also, the cause of IBD pathomorphism can undoubtedly be considered the influence of antibacterial therapy, which was used everywhere in almost all cases of SARS-Cov-2 infection, especially in the period 2020-2021, which could lead to a violation of the intestinal microbiota, as well as a subsequent increase in IBD activity.

Conclusion. Thus, inflammatory bowel disease and current therapy do not affect the risk of SARS-Cov-2 infection and/or the severity of COVID-19, just as infection also does not affect IBD activity or outcomes. At the same time, we have identified risk factors for the development of infection and complications characteristic of a severe course according to the world literature.

Sample. *The heterogeneity of the sample was due to the contingent of patients observed in academic centers; in St. Petersburg, the majority of patients were male.*

Conflict of interests. *No conflict of interest*

Gratitude to Acting Head of the Department of Therapy 1 of the Research Institute of Cardiology and Internal Diseases (Almaty, Kazakhstan) Khan O.R.

References:

1. *Ananthakrishnan A.N., McGinley E.L.* Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis 2013;7:107–112.
2. *Brenner E.J., Ungaro R.C., et al.* Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. Gastroenterology 2020; 159:481–491.
3. *Cai Z., Wang S., Li J.* Treatment of Inflammatory Bowel Disease: A Comprehensive Review. Front. Med. 2021, 8:765474. doi: 10.3389/fmed.2021.765474
4. *Chena F., Chenb W., Chen J. et al.* Clinical features and risk factors of COVID-19-associated liver injury and function: A retrospective analysis of 830 cases. Annals of hepatology, 21 (2021) 100267.
5. *Clift A.K., Coupland C.A.C., Keogh R.H. et al.* Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study // BMJ. 2020; 371:m3731 doi:10.1136/bmj.m3731
6. Coronavirus infection COVID-19 in adults (6th edition), Clinical protocol 166, July 25, 2022, Republic of Kazakhstan.
7. COVID-19 Map. Johns Hopkins Coronavirus Resource Center. Accessed December 17, 2020.
8. *Donoghue M., Hsieh F., Baronas E., et al.* A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9 // Circ Res. 2000 Sep 1;87(5):E1-9. doi: 10.1161/01.res.87.5.e1.
9. *Garg M., Burrell L.M. et al.* Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: a pilot study // J Renin Angiotensin Aldosterone Syst 2015;16:559–69.
10. *Garg M., Royce S.G., Tikellis C., et al.* Imbalance of the renin-angiotensin system may contribute to inflammation and fibrosis in IBD: a novel therapeutic target? // Gut 2020;69:841–51.
11. *Hashimoto T., Perlot T., Rehman A., et al.* ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation // Nature 2012;487:477–81.
12. *Keidar S., Kaplan M., Gamliel-Lazarovich A.* ACE2 of the heart: From angiotensin I to angiotensin (1-7) // Cardiovasc Res. 2007 Feb 1;73(3):463-9. Epub 2006 Sep 19. PMID: 17049503.
13. *Kirchgesner J., Lemaitre M., Carrat F., et al.* Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases // Gastroenterology 2018; 155:337–346.e10.
14. *Lin Simeng, Lau Louis H.S., Chanchlani Neil et al.* Recent advances in clinical practice: management of inflammatory bowel disease during the COVID-19 pandemic // Gut 2022; 71:1426–1439. doi:10.1136/gutjnl-2021-326784
15. *Long M.D., Martin C., Sandler R.S., et al.* Increased risk of pneumonia among patients with inflammatory bowel disease // Am J Gastroenterol 2013;108:240–248.
16. *Ma C., Lee J.K., Mitra A.R., et al.* Systematic review with meta-analysis: efficacy and safety of oral Janus kinase inhibitors for inflammatory bowel disease // Aliment Pharmacol Ther 2019;50:5–23.
17. *Macaluso F.S., Orlando A.* COVID-19 in patients with inflammatory bowel disease: A systematic review of clinical data // Dig Liver Dis. 2020 Nov;52(11):1222-1227. doi: 10.1016/j.dld.2020.09.002. Epub 2020 Sep 6. PMID: 32928672; PMCID: PMC7474894.
18. *Onder G., Rezza G., Brusaferro S..* Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy // JAMA. 2020 May 12;323(18):1775-1776. doi: 10.1001/jama.2020.4683. Erratum in: JAMA. 2020 Apr 28;323(16):1619. PMID: 32203977.
19. *Rahman A., Sathi N.J.* Risk factors of the severity of COVID-19: A meta-analysis // Int J Clin Pract. 2021 Jul;75(7):e13916
20. *Ramos G.P., Papadakis K.A.* Mechanisms of Disease: Inflammatory Bowel Diseases // Mayo Clin Proc. 2019 Jan;94(1):155-165. doi: 10.1016/j.mayocp.2018.09.013. PMID: 30611442; PMCID: PMC6386158.
21. *Singh S., Khan A., et al.* Risk of Severe Coronavirus Disease 2019 in Patients With Inflammatory Bowel Disease in the United States: A Multicenter Research Network Study // Gastroenterology. 2020 Oct;159(4):1575-1578.e4. doi: 10.1053/j.gastro.2020.06.003. Epub 2020 Jun 6. PMID: 32522507; PMCID: PMC7702184.
22. *Tanabayeva A.S. et all.* Clinical and epidemiological features of COVID-19 in inflammatory bowel diseases in the Republic of Kazakhstan, poster within the framework of the Central Asian Gastroweek, http://kasl.kz/event/poster?id=17688&article=33977
23. *Tinsley A., Williams E., Liu G., et al.* The incidence of influenza and influenza-related complications in inflammatory bowel disease patients across the United States: 1833 // Am J Gastroenterol 2013:108.
24. *Tripathi Kartikeya, Brewer Gala Godoy, Nguyen Minh Thu et al.* COVID-19 and Outcomes in Patients With Inflammatory Bowel Disease: Systematic Review and Meta-Analysis // Inflamm Bowel Dis. 2021 Oct 27 : izab236.
25. *Tursi A., Lopetuso L.R., Vetrone L.M. et al.* SARS-CoV-2 infection as a potential trigger factor for de novo occurrence of inflammatory bowel disease // Eur J Gastroenterol Hepatol. 2022 Aug; 34(8): 883–884.
26. *Ualiyeva A., Oshibayeva A., Kaibullayeva J.* Determination of environmental factors associated with inflammatory bowel disease in Kazakhstan: a case-control study // Nauka i Zdravookhranenie [Science & Healthcare]. 2020, (Vol.22) 4, pp. 97-104. doi 10.34689/SH.2020.22.4.010
27. *Ungaro R.C., Brenner E.J., et al.* Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) Research Group. Impact of Medications on COVID-19 Outcomes in Inflammatory Bowel Disease: Analysis of Over 6,000 Patients from an International Registry // Gastroenterology 2022; 162:316–319

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