



Clinical Course of COVID-19 in Patients with Inflammatory Bowel Disease: Regional Experience

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Aim: to study the course of COVID-19 in patients with inflammatory bowel diseases (IBD) using the example of the region of the Republic of Tatarstan.

Material and methods. The study included 101 patients diagnosed with IBD and COVID-19, who were observed in two infectious diseases hospitals in Kazan (Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan and City Clinical Hospital No. 7) and on an outpatient basis from April 2020 to March 2022. All patients underwent physical examination, laboratory and instrumental diagnostic methods, including a PCR test for SARS-CoV-2. Chest computed tomography was performed in patients with clinical signs of moderate to severe COVID-19.

Results. Ulcerative colitis (UC) was diagnosed in 60 (59.4 %) patients, Crohn's disease (CD) — in 41 (40.6 %) patients. The mean age of the patients was 41.0 ± 14.7 years, of which 59 (58.4 %) were men and 42 (41.6 %) were women. A comparative analysis of patients with and without IBD and CT-verified lung disease was carried out. It was found that the development of viral pneumonia was influenced by age over 55 years (39.2 ± 9.7 vs. 46.3 ± 10.6 , $p < 0.05$), increased Body Mass Index (BMI) (23.1 ± 5.35 vs. 30.25 ± 6.17 , $p < 0.05$), hypertension (6 (8.3 %) vs. 8 (27.6 %), $p < 0.05$), diabetes mellitus (2 (2.7 %) vs. 5 (17.2 %), $p < 0.05$), the use of corticosteroids in the treatment of IBD (8 (11.1 %) vs. 10 (34.5 %), $p < 0.05$). In a comparative analysis of patients with IBD and COVID-19 from the SECURE-IBD database and own data, it was found that the average age of patients was comparable (42.7 vs 41.0). At the same time, in our group of male patients, there were slightly more people with DM, increased BMI, and an active course of IBD. The proportion of hospitalized patients was higher. In our cohort, there were fewer patients receiving biological therapy, but more patients on 5-aminosalicylic acid (5-ASA) and systemic corticosteroids. At the same time, lethal outcomes were comparable.

Conclusion. In patients with IBD, the development of viral pneumonia was influenced by known risk factors for COVID-19: age over 55 years ($p < 0.05$, odds ratio (OR) 3.153), increased BMI ($p < 0.05$, OR 1.667), hypertension ($p < 0.05$, OR 2.724), diabetes ($p < 0.05$, OR 1.489), as well as the use of systemic corticosteroids ($p < 0.05$, OR 1.5).

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, novel coronavirus infection, COVID-19

Conflict of interest: The work is carried out within the framework of the Grant of the President of the Russian Federation to support the leading scientific schools of the Russian Federation (theme "Development of technologies for the health care of patients with immunoinflammatory diseases during the COVID-19 pandemic" (NSh-4321.2022.3).

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Течение COVID-19 у пациентов с воспалительными заболеваниями кишечника: опыт региона

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Цель исследования: изучение течения COVID-19 у пациентов с воспалительными заболеваниями кишечника (ВЗК) на примере региона Республики Татарстан.

Материал и методы. В исследование был включен 101 пациент с диагнозом ВЗК и COVID-19, наблюдавшийся в двух временных инфекционных госпиталях г. Казани (ГАУЗ «РКБ МЗ РТ» и ГАУЗ «ГКБ № 7») и амбулаторно с апреля 2020 по март 2022 года. Всем пациентам проводились объективный осмотр, лабораторные и инструментальные методы диагностики, включая ПЦР-тест на SARS-CoV-2. Пациентам с клиническими признаками среднетяжелого и тяжелого течения COVID-19 проводилась компьютерная томография легких.

Результаты. В исследование были включены пациенты с верифицированными диагнозами БК 41 (40,6 %) и ЯК 60 (59,4 %). Средний возраст пациентов составил $41,0 \pm 14,7$ года, из них мужчин — 59 (58,4 %), женщин — 42 (41,6 %). Был проведен сравнительный анализ пациентов с ВЗК и КТ-верифицированным поражением легких и без такового. Было выявлено, что на развитие вирусной пневмонии влияли возраст старше 55 лет ($39,2 \pm 9,7$ против $46,3 \pm 10,6$, $p < 0,05$), повышенный индекс массы тела (ИМТ) ($23,10 \pm 5,35$ против $30,25 \pm 6,17$, $p < 0,05$), наличие гипертонической болезни (ГБ) (6 пациентов (8,3 %) против 8 пациентов (27,6 %), $p < 0,05$), сахарного диабета (СД) (2 пациента (2,7 %) против 5 пациентов (17,2 %), $p < 0,05$), применение глюкокортикостероидов (ГКС) при лечении ВЗК (8 пациентов (11,1 %) против 10 пациентов (34,5 %), $p < 0,05$). При сравнительном анализе пациентов с ВЗК и COVID-19 из базы данных SECURE-IBD и собственных данных было выявлено, что средний возраст пациентов был сопоставим ($42,7$ против $41,0$). При этом в нашей группе пациентов мужского пола лиц с СД, повышенным ИМТ, активным течением ВЗК было несколько больше. Доля госпитализированных пациентов была выше. В нашей когорте было меньше пациентов, получающих генно-инженерные биологические препараты, но больше пациентов, получающих препараты 5-аминосалициловой кислоты и системные ГКС. При этом летальные исходы были сопоставимы.

Выводы. У пациентов с ВЗК на развитие вирусной пневмонии влияли известные факторы риска COVID-19: возраст старше 55 лет ($p < 0,05$, отношение шансов (ОШ) 3,153), повышение ИМТ ($p < 0,05$, ОШ 1,667), ГБ ($p < 0,05$, ОШ 2,724), СД ($p < 0,05$, ОШ 1,489), а также применение системных ГКС ($p < 0,05$, ОШ 1,5).

Ключевые слова: воспалительные заболевания кишечника, язвенный колит, болезнь Крона, новая коронавирусная инфекция, COVID-19

Конфликт интересов. Работа выполняется в рамках гранта Президента Российской Федерации по поддержке ведущих научных школ Российской Федерации. Тема: «Разработка технологий здоровьесбережения пациентов с иммуновоспалительными заболеваниями в период пандемии COVID-19». Номер гранта: НШ-4321.2022.3.

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Introduction

COVID-19 is an infectious respiratory disease with a wide range of manifestations and outcomes, which is caused by the novel coronavirus SARS-CoV-2. The clinical picture of the novel coronavirus infection is variable and in most cases corresponds to the course of an acute respiratory infection, but the risk of severe illness and death is higher in the elderly and in people with comorbidities [1].

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing diseases of the gastrointestinal tract (GIT) of an immune origin [2, 3]. For the treatment of IBD, glucocorticosteroids, immunosuppressive therapy, biologic drugs, as well as small molecules are used, some of which have found their application in the treatment of moderate and severe forms of COVID-19 [4].

In 2020, an international database SECURE-IBD was created, designed to assess the course of a novel coronavirus infection in patients with IBD and to monitor the outcomes of COVID-19 in patients in this group. According to SECURE-IBD, the incidence of novel coronavirus infection in patients

with IBD is comparable to that in the general population [5].

Older age, male sex, IBD activity, corticosteroid use, and comorbidities are known to be associated with an increased risk of hospitalization and death [6, 7]. J. Sperger et al. (2021) [4] showed that the use of prednisone at a daily dose of 40 mg or more was associated with a tenfold increase in deaths, while biologic therapy, on the contrary, was associated with a lower risk of adverse outcomes of COVID-19.

The aim of our research was to study the clinical course of COVID-19 in patients with IBD using the example of the Republic of Tatarstan.

Material and methods

The study included 101 patients diagnosed with IBD and COVID-19, among them 25 patients (24.8 %) observed in two infectious diseases hospitals in Kazan and 76 (75.2 %) outpatients observed from April 2020 to March 2022. The research was not a part of a clinical study. Permission was obtained from the administration of the Republican Clinical Hospital of the Ministry of Health of the Republic of

Tajikistan and the State Clinical Hospital No. 7 to work with primary medical documentation.

The study was approved by the Central Commission on Bioethics under the Ministry of Health of the Russian Federation (extract from Protocol No. 1 dated April 12, 2022).

The diagnosis of IBD was made in accordance with the national clinical guidelines for the diagnosis and treatment of ulcerative colitis and Crohn's disease [2, 3]. The diagnosis of COVID-19 was made in accordance with the temporary guidelines for the prevention, diagnosis and treatment of a new coronavirus infection.

All patients underwent physical examination, laboratory and instrumental diagnostic methods, including a PCR test for SARS-CoV-2. Computed tomography (CT) of the chest was performed in patients with clinical signs of moderate to severe COVID-19. Saturation less than 94 % was considered as respiratory failure.

Mathematical and statistical processing of the results was carried out using the IBM SPSS Statistics Data Editor version 23 software. To describe the qualitative nominal features, their absolute and relative frequencies were determined. In case of normal distribution, the results are presented as $M \pm SD$, where M is the mean value, SD is the standard deviation. In this case, to compare groups by quantitative characteristics, a parametric method was used with the calculation of the Student's t -test for independent groups (assuming equal variances in groups). If the distribution differed from normal, the data are presented as a median (Me) and an interquartile range [$Q1$; $Q3$], where $Q1$ is the 25th quartile, $Q3$ is the 75th quartile. In this case, the significance of intergroup differences was checked by the Mann–Whitney U -test, and Wilcoxon test in paired measurements.

The χ^2 test was used to identify frequency differences. If at least one of the compared groups had less than 5 cases, Fisher's exact test (two-tailed test) was used. If the absolute frequencies were less than 10 but greater than 5, the χ^2 test was used with Yates' correction for continuity.

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Results

UC was diagnosed in 60 (59.4 %) patients, CD – in 41 (40.6 %) patients. The mean age of the patients was 41.0 ± 14.7 years, of which 59 (58.4 %) were males and 42 (41.6 %) were females. The average

duration of the disease in patients with UC was 6.4 ± 3.2 years, in patients with CD – 7.3 ± 4.7 years.

Proctitis was diagnosed in 10 (16.7 %), left-sided colitis – in 11 (18.3 %), total colitis – in 39 (65 %) patients. According to the location of the lesion, the distribution of patients with CD was as follows: terminal ileitis – 11 (26.8 %), colitis – 15 (36.6 %), ileocolitis – 15 (36.6 %).

At the time of the onset of COVID-19 in UC, remission was observed in 20 (33.3 %) patients, exacerbation – in 40 (66.7 %) patients. In CD, 17 (41.5 %) patients were in remission, 24 (58.5 %) had an exacerbation.

The therapeutic approach to the management of IBD was determined by the clinical course of IBD. Depending on this, the main drugs used were 5-ASA – 45 patients (44.5 %), steroids (prednisolone) – 18 (17.8 %), immunosuppressants (azathioprine, methotrexate) – 11 (10.9 %), biological therapy and small molecules – 19 (18.8 %) (infliximab – 7 (36.8 %), certolizumab – 5 (26.3 %), golimumab – 1 (5.3 %), vedolizumab – 2 (2.0 %)), tofacitinib – 2 (2.0 %), adalimumab – 2 (2.0 %), as well as combinations of these drugs).

One third of patients (32 %) had at least one comorbidity other than IBD. The most common comorbidities were overweight and obesity – 28 (27.7 %), hypertension – 14 (13.8 %), including the combination with coronary artery disease and arrhythmias – 5 (4.9 %), diabetes mellitus – 7 (6.9 %), COPD – 2 (2.0 %), right middle lobectomy due to aspergilloma – 1 (1.0 %), chronic kidney disease – 1 (1.0 %).

8 patients (7.9 %) with comorbidities had a mild course of COVID-19, 11 (10.9 %) had a moderate course, 3 (3.0 %) had a severe course.

Next, we identified the COVID-19 complaints specific to IBD patients. The most common complaints of patients when seeking medical help were general weakness in 75 patients (74.3 %), diarrhea in 71 (70.3 %), dysosmia/dysgeusia in 71 (70.3 %), fever in 69 (68.3 %), cough – 58 (57.4 %), blood in the stool – 46 (45.5 %), abdominal discomfort – 28 (27.7 %), chest pain – 20 (19.8 %), shortness of breath – 16 (15.8 %), and nausea – 6 (5.9 %) (Fig. 1).

76 (75.2 %) patients had mild COVID-19, 20 (19.8 %) had moderate severity, and 5 (5.0 %) had severe COVID-19. The duration of hospitalization was 7–45 days. 5 patients were treated in the intensive care unit with mechanical ventilation.

Indications for CT were found in 32 patients: CT-0 stage was detected in 3 patients (9.4 %), CT-1 – in 16 (50 %); CT-2 – 7 (21.9 %); CT-3 – 1 (3.1 %); CT-4 – 5 (15.6 %).

A comparative analysis of IBD patients with and without CT-verified lung disease was performed. It

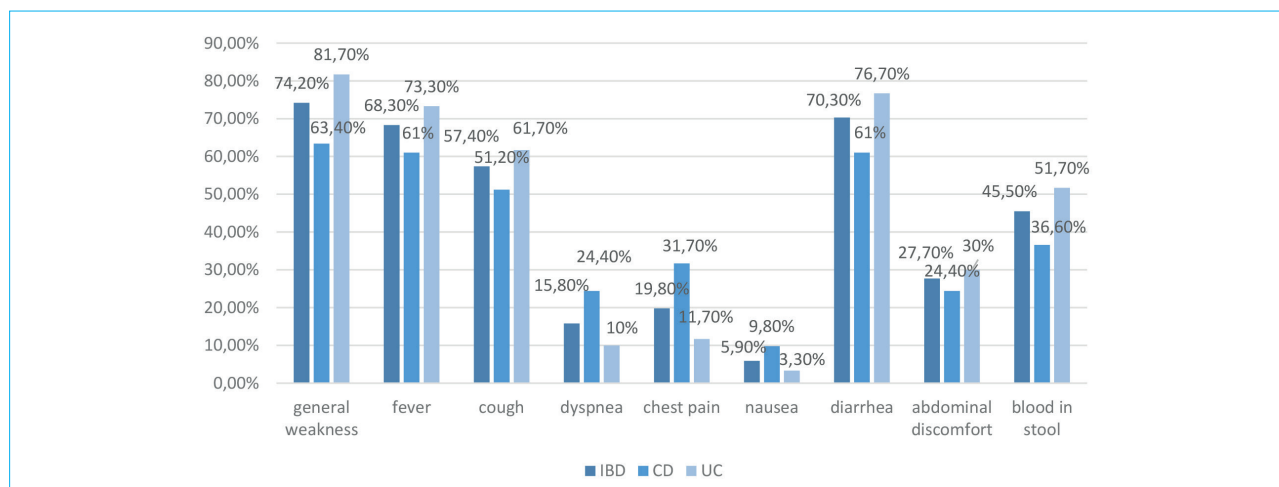


Fig. 1. Symptoms of the debut of COVID-19 in patients with IBD

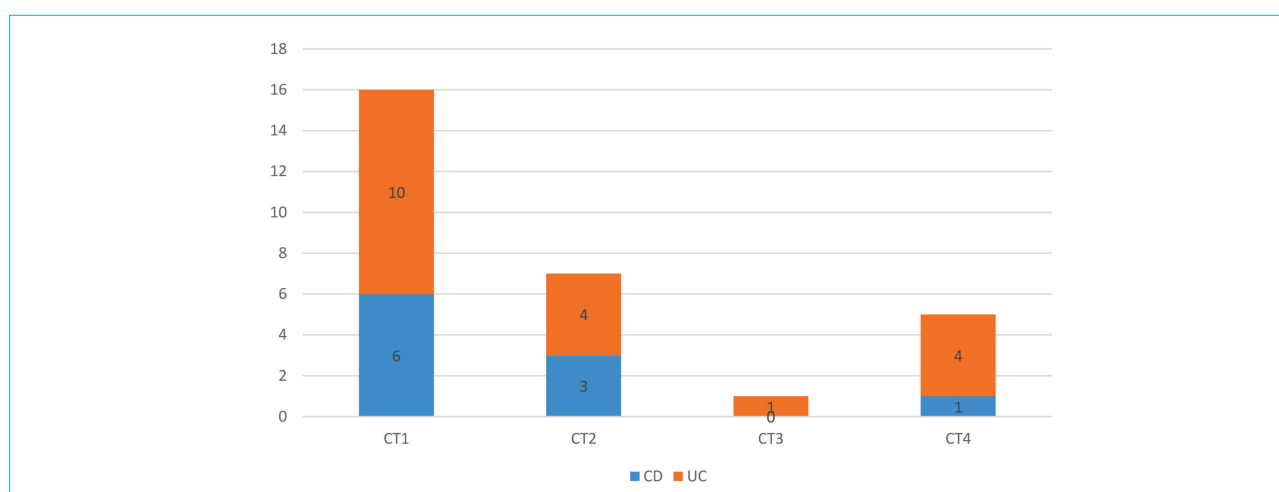


Fig. 2. CT scan stages in patients with IBD

Table 1. Comparative analysis of the main risk factors for COVID-19 in IBD patients with and without CT-verified lung disease

Risk Factors	CT0 (n = 72)	CT+ (n = 29)	p
Age > 55 years (M ± δ)	39.2 ± 9.7	46.3 ± 10.6	0.001*
Duration of IBD (year) (M ± δ)	5.7 ± 4.8	5.9 ± 5.1	0.674
IBD disease activity, n (%)	44 (61.1)	20 (68.9)	0.642
BMI, kg/m ² (M ± δ)	23.10 ± 5.35	30.25 ± 6.17	0.043*
Diabetes mellitus, n (%)	2 (2.7)	5 (17.2)	0.038*
Arterial hypertension, n (%)	6 (8.3)	8 (27.6)	0.013*
Systemic corticosteroids, n (%)	8 (11.1)	10 (34.5)	0.048*
Steroid dose >15 mg/d, n (%)	3 (4.2)	6 (20.7)	0.147
Biologics, n (%)	15 (27.6)	4 (13.8)	0.081
5-Aminosalicylates, n (%)	27 (37.5)	18 (62)	0.101
Azathioprine, n (%)	5 (6.9)	6 (20.7)	0.378
C-reactive protein, mg/l	41.50 [9.87; 56.70]	62.80 [9.85; 93.80]	0.691
D-dimer, mg/l	0.44 [0.36; 0.57]	0.76 [0.54; 1.70]	0.487

Note. * $p < 0.05$. CT – computed tomography, n – number of patients, CRP – C-reactive protein.

Table 2. Risk factors associated with moderate to severe COVID-19

Risk factors	Univariate OR (95 % CI)	<i>p</i>
Age > 55 years	3.153 (1.080–9.204)	0.05*
Arterial hypertension	2.724 (1.842–8.811)	0.05*
BMI, kg/m ² (<i>M</i> ± <i>δ</i>)	1.667 (0.651–4.269)	0.05*
Systemic corticosteroids	1.5 (0.466–4.831)	0.05*
Diabetes mellitus	1.489 (0.517–11.974)	0.05*

Note. * *p* < 0.05. CT – computed tomography.

was found that the development of viral pneumonia was associated with the age over 55 years (39.2 ± 9.7 versus 46.3 ± 10.6 , $p < 0.05$), increased BMI (23.1 ± 5.35 versus $30, 25 \pm 6.17$, $p < 0.05$), hypertension (6 patients (8.3 %) versus 8 patients (27.6 %), $p < 0.05$), diabetes mellitus (2 patients (2, 7 %) versus 5 patients (17.2 %), $p < 0.05$), the use of corticosteroids in the treatment of IBD (8 patients (11.1 %) versus 10 patients (34.5 %), $p < 0.05$). In our patients, the development of pneumonia was not affected by the activity of IBD as well as by the dose of systemic corticosteroids (Table 1).

When assessing risk factors using univariate analysis, it was found that the age over 55 years (odds ratio (OR): 3.153, 95 % confidence interval (CI): 1.080–9.204, $p = 0.05$) and the history of AH (OR: 2.724, 95 % CI: 1.842–8.811, $p = 0.05$) were associated with moderate and severe COVID-19 (Table 2).

In a comparative analysis of patients with IBD and COVID-19 from the SECURE-IBD database [8] and our own data, it was found that the average age of patients was comparable (42.7 vs. 41.0). At the same time, in our subgroup of male patients, there were slightly more people with DM, increased BMI, and an active course of IBD. The proportion of hospitalized patients was higher. In our cohort, there were fewer patients receiving biologics, but more patients on 5-ASA and systemic corticosteroids. At the same time, lethal outcomes were comparable (Table 3).

We performed a detailed analysis of the lethal outcomes of 5 patients with IBD, four of whom were men. The mean age of patients was 67.2 years [35; 86], 4 (80 %) patients were over 65 years. Concomitant hypertension was observed in 4 patients, overweight – in 3 patients, DM – in 2 patients, and chronic lymphocytic leukemia in 1 patient. Four patients had UC, one had CD (Table 4).

At the time of diagnosis of COVID-19, all patients had an exacerbation of IBD, of which three were hospitalized with a severe exacerbation of UC. Patient No. 2 underwent colectomy due to total colitis complicated by multiple perforations, interintestinal abscesses, retroperitoneal phlegmon, widespread serous peritonitis. Patient No. 1, 35 years old, on the day of visit due to COVID-19, had respiratory failure grade 2 and CT-4, received systemic corticosteroids 40 mg/day, due to exacerbation of UC. With regard to the ongoing IBD therapy, 2 patients received 5-ASA, 3 – systemic corticosteroids, 1 – a combination of 5-ASA + systemic corticosteroids.

All deceased patients were diagnosed with pneumonia (CT 3–4), with the development of acute respiratory distress syndrome (ARDS) and severe respiratory failure, which required tracheal intubation and invasive mechanical ventilation (IMV).

Currently, prospective follow-up of patients who have undergone COVID-19, continues: 12 (20 %) patients were vaccinated with Sputnik V, 10 (16.7 %) – with CoviVac, 5 (8.3 %) were revaccinated with Sputnik Light.

Table 3. Comparison of patients with IBD from the SECURE-IBD database and own data

	Age in years, mean	Males, <i>n</i> (%)	IBD disease activity, <i>n</i> (%)	BMI, kg/m ² (%)	CD (%)	UC (%)	Hospitalization (%)	Mortality (%)	AH (%)	DM (%)	CKD (%)	COPD (%)	Biologics (%)	5-ASA (%)	Systemic corticosteroids (%)
SECURE-IBD	42.7	50.6	44.5	16.0	56.0	44.0	26.4	3.1	12.6	5.8	3.73	3.55	59.0	31.0	10.0
Own data	41.0	58.4	63.4	23.1	40.6	59.4	31.7	4.9	13.8	9.9	1.0	2.0	18.8	44.5	17.8

Note. * SECURE-IBD data as of 02/01/2022.

Table 4. Characteristics of patients with IBD and COVID-19 with a lethal outcome based on Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan

N	Age/ gender	IBD classifi- cation	BMI	AH	IHD	DM	Oncology	IBD activity	IBD medications	CT
1	35/м	UC	28.1	-	-	-	-	Active	Prednisolone	4
2	68/м	UC	29.6	+	-	-	-	Active Colectomy	GCS 5-ASC	3
3	86/ж	UC	22.7	+	-	-	+ chronic lymphocytic leukemia	Active	Prednisolone	3
4	66/м	CD	27.5	+	+	+	-	Active	Prednisolone	2
5	81/м	UC	22.6	+	+	+	-	Active	5-ASC	1→3

Discussion

Based on our data, the clinical presentation of COVID-19 in patients with IBD is variable.

In a comparative analysis of patients with IBD and COVID-19 from the SECURE-IBD database [8] and our own data, it was found that the average age of patients was comparable. At the same time, in our group of male patients, there were slightly more people with DM, increased BMI, and an active course of IBD. The proportion of hospitalized patients was higher. In our cohort, there were fewer patients receiving biologics, but more patients on 5-ASA and systemic corticosteroids. At the same time, lethal outcomes were comparable.

Our data were comparable to those of Rajen Parekh et al. (2021) [6] and Ricciuto A. et al. (2021)

[7], and confirmed that older age, male sex, IBD activity, corticosteroid use, and comorbidities were associated with an increased risk of hospitalization and death.

Conclusion

1. Patients with IBD at the onset of COVID-19 are characterized by a high frequency and severity of both respiratory (up to 57.4 %) and gastrointestinal symptoms (up to 70.3 %).

2. In patients with IBD, the development of viral pneumonia was associated with the known risk factors for COVID-19: age over 55 years, increased BMI, history of hypertension, diabetes, and use of systemic corticosteroids.

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