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## Research Article

# CHARACTERISTICS OF INTESTINAL MICROBIOTSENOSIS IN COVID-19 PATIENTS

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## ABSTRACT

The purpose of this study is to analyze changes in the intestinal microflora of patients with COVID-19 in foreign countries and the role of microorganisms in the development of dysbacteriosis. Patients with Covid-19 usually complain of fever, cough, expectoration, shortness of breath, headache, and fatigue, but at the same time, some patients with Covid-19 experience gastrointestinal symptoms such as diarrhea, anorexia, nausea, and vomiting, complaints from the gastrointestinal tract. The literature review analyzed the etiological causes of intestinal dysbacteriosis in COVID-19. It has been established that in the intestinal microflora of patients with COVID-19, there is an increase in the number of opportunistic and pathogenic bacteria and a decrease in the number of beneficial microorganisms.

## KEYWORDS

COVID-19, SARS-CoV-2, intestinal microflora, diarrhea, bacteria

## INTRODUCTION

Today SARS-CoV-2 caused COVID-19 disease was officially declared a pandemic on March 11, 2020 by the World Health Organization as a worldwide outbreak of coronavirus infection. To date, 390 961 200 people worldwide have been infected with COVID-19, and 5 725 993 have died as a result of the pandemic (WHO 05.02.2022y) [45]. which requires the development of laboratory tests, treatment methods and prevention measures for COVID-19. [2,32,35]. Coronavirus infection (COVID-19) is a new strain of the SARS CoV-2 coronavirus family that spreads by airborne and household contact way, prone to damage lung tissue. It can range from asymptomatic virus carriers to severe clinical manifestations of the disease, as an infectious disease, intoxication, inflammation of the upper and lower respiratory tract [35] i.e. bilateral pneumonia (viral diffuse alveolar injury with microangiopathy), the development of acute respiratory distress syndrome were noted [27]. However, with COVID-19, damage has been observed to organs and systems other than the body's respiratory organs and systems, including the digestive system. The gastrointestinal tract (GIT) can serve as an "entry gate for infection" along with respiratory tract [7,15,17,19]. Changes in the composition of the intestinal microflora in patients with COVID-19 infection have been identified in several studies [4,28,30].

## MATERIALS AND METHODS

In order to write this article other articles, literature, and research findings on the intestinal microflora in COVID-19 have been analyzed.

## RESULTS

As of January 31, 2020, the team of Chinese researchers led by Dr. Zhong studied 1,099 Chinese patients, and diarrhea was diagnosed in 3.8% of them [9]. Similarly, Huang et al found that diarrhea was the main symptom in one of every 41 patients, and that the incidence of diarrhea was 2.4%. аниқлашди [12]. In the later stages of the COVID-19 pandemic, a significant increase in the number of patients with diarrhea was observed, indicating an increase in the incidence of diarrhea. 49.5% of the patients admitted to Wuhan Hospital in Hubei Province of China with Covid-19 infection were patients with diarrhea [3].

Evaluating the results of follow-up of patients in China, it can be noted that the lesions of the gastrointestinal tract in Covid-19 vary. Symptoms of diarrhea in Covid-19 have also been reported in the pediatric population, with diarrhea and vomiting occurring in 8.8% and 6.4% of sick children, respectively, and in such patients (both adults and children) respiratory symptoms of coronavirus infection may appear later than gastroenterological symptoms or may not be visible at all [11,16,26]. A study of 140 patients with Covid-19 in Wuhan showed that 39.6% of these patients had gastrointestinal symptoms, 24 had 17.3% nausea, 18 had 12.9% diarrhea and 7 had 5% vomiting. 74 patients with Covid-19 with gastrointestinal symptoms in Zhejiang Province, 53 had 71.6% diarrhea alone, 11 had 14.9% vomiting, and 10 had 13.5% nausea. A meta-analysis involving 4,243 patients from China, Singapore, South Korea, the United Kingdom, and the United States showed that 17.6% of patients had gastrointestinal symptoms, 26.8% had anorexia, 12.5% had diarrhea, 10.2% had nausea and vomiting, 9.2% had abdominal pain and discomfort, and other symptoms were observed in 23.7% of patients. The frequency of diarrhea ranged from 2.0% to 10.1%, and nausea and



vomiting ranged from 1.0% to 10.1% [25]. Gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal pain occur in approximately 20–40% of patients with Covid-19 infection [1,33,46]. We analyzed 19 published scientific studies on Covid-19 disease that was associated with diarrhea, nausea, abdominal pain, vomiting, anorexia, and bleeding. Of the 19 scientific papers, 13 were from China, 4 from the United States, 1 from Singapore, and 1 from Europe. In our analysis, the symptom of diarrhea was the most common, ranging from 2% to 33.7% of all patients. The mean duration of diarrhea in patients with Covid-19 was 1 to 9 days [14]. Other common gastrointestinal symptoms include anorexia (341/2914, 11.7%), nausea (253/2914, 8.7%), and vomiting (131/2914, 4.5%), pain (90/2914, 3.1%) and bleeding (5/ 2914, 0.2%). Symptoms of diarrhea were reported more frequently than at the time of hospitalization [15]. Recently, we reported a strong link between diarrhea and disease severity [10]. These data suggest that diarrhea symptoms may indicate the severity of Covid-19 [24].

Earlier (January 2021), U.S. researchers introduced the results of a study on the medical portal Biocodex, which showed that in COVID-19 disease, a disruption of the intestinal microflora, is associated with the disease. The study found that symptoms associated with the disease, such as vomiting, nausea, and diarrhea, were often observed when the disease was severe. In a study of 318 patients diagnosed with COVID-19, 34.8% had gastrointestinal symptoms, including 33.7% with diarrhea. It is worth noting that gastrointestinal symptoms, such as diarrhea can sometimes occur before fever and respiratory symptoms.

According to British expert Professor Tim Spector (2021), in patients with severe COVID-19 disease, the intestinal microflora is severely damaged and the state of the intestinal microbiome is of great importance in

protecting against coronavirus and many other diseases.

According to Anna Balandina (01.22.2021), an infectious disease doctor in the Russian Federation, the disruption of the intestinal microflora may be due to the entry of SARS-CoV-2 virus into the intestinal epithelial cell and the presence of special receptors on its surface. The virus affects both respiratory tract cells and gastrointestinal tract cells through these receptors. Therefore, the cells die and the processes of cell digestion, absorption of nutrients are disrupted. The digestive system can serve as a gateway for other infections, which slows down the recovery process after COVID-19 disease. The term “intestinal virus” began to appear in the scientific literature. If the presence of pathogenic viruses in the human gut has been proven more than a century ago, their effects on human homeostasis have only recently been studied. The result of scientific studies is that pathogenic viruses belonging to the families Adenoviridae, Picornaviridae, Reoviridae, Mimivirus, affecting physiological processes in the intestine can lead to changes in the composition of the intestinal microflora in terms of quantity and quality [22].

The gastrointestinal tract has been shown to be an extrapulmonary site for replication of SARS-CoV-2 virus because angiotensin-converting enzyme receptors (ACE2) are expressed not only on type II pneumocyte membranes but also on the apical surface of intestinal epithelial cells. This suggests that SARS-CoV-2 is transmitted through the fecal-oral mechanism [5,21]. The SARS-CoV-2 virus enters the gastrointestinal tract through the mechanism of fecal-oral transmission, and as a result of the virus binding to intestinal cells through ACE2 receptors, it manifests clinical signs of the gastrointestinal tract. Zuo and others (2021) found that almost half of the patients with Covid-19 infection



had SARS-CoV-2 virus in their fecal samples, and in patients which SARS-CoV-2 virus positive conditioned, the amount of pathogens such as *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii* might be high [6,8,33,47,48]. Previously, it was reported that SARS-CoV-2 virus was found in fecal samples (four out of eight patients) regardless of the presence of diarrhea symptoms [15]. In addition, another study showed that SARS-CoV-2 RNA was found in the fecal samples of 22 (52.4%) patients out of 42 Covid-19 patients with gastrointestinal symptoms. SARS-CoV-2 RNA was found in the fecal samples of 9 (39.1%) patients out of 23 Covid-19 patients without gastrointestinal symptoms [31]. Fecal samples of patients with severe Covid-19 infection had higher levels of conditionally pathogenic bacteria, such as *Morganella morganii*, *Collinsella aerofaciens*, *Streptococcus infantis* and *Collinsella tanakaei*. *Bacteroides stercoris*, *Parabacteroides merdae*, *Lachnospiraceae*, and *Alistipes onderdonkii* bacteria were more prevalent in the fecal samples of patients without signs of Covid-19 infection [33].

In September 2020, Koloskova E.A. published data on the examination of fecal samples of 15 patients with SARS-CoV-2 by sequencing of 16sRNA. It is detected that in such patients there is a decrease in the amount of commensal bacteria (*Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia*, *Lachnospiraceae*) and conditionally increase in pathogenic bacteria (*Clostridia hathewayi*, *Actomyces viscosus* and *Bacteroides nordii*, *Candida albicis*, *Candida albicans*, *Candida albicans*). Thus, bacteria of *Clostridium hathewayi* (Firmicutes type), *Bacteroides nordii* (Bacteroidetes type) and *Actinomyces viscosus* species were found to be significantly higher in the examined patients than in healthy volunteers, indicating that the severity of Covid-19 disease is

directly related to conditionally pathogenic bacteria (*Clostridium ramosum*, *Clostridium hathewayi*) [37].

In January 2021, a study conducted by a group of Chinese scientists involving 100 patients with COVID-19 was published. Accordingly, changes in the composition of the intestinal microbiocenosis in patients were confirmed to occur earlier. Examination of the feces of patients by 16sRNA sequencing method showed a decrease in the number of bacterial species of *Faecalibacterium prausnitzii* and *Eubacterium rectale* (type Firmicutes), *Bifidobacterium adolescentis* (Actinobacteria type) compared to healthy people. Intestinal dysbacteriosis associated with decreased levels of *Lactobacillus* and *Bifidobacterium* has been observed in patients with Covid-19 [29].

Increased levels of *Collinsella*, *Streptococcus*, *Morganella*, *Coprobacillus*, *Clostridium ramosum*, and *Clostridium mathewayi* were increased in patients with severe Covid-19 disease, and *parabacteroides*, *Bacteroides*, *Alistipes*, *Lachnospiraceae*, *F.Prausnitzii* were increased in mildly ill patients [21,33]. Moreira-Rosario and others [18] studied the effect of Covid-19 disease on changes in the composition of the intestinal microbiocenosis. The results of the study revealed changes in the ratio of Firmicute and Bacteroid. The authors also found a decrease in the number of butyrate-forming bacteria belonging to the family *Lachnospiraceae* (*Reseburia* and *Lachnospira*), a decrease in the amount of bacteria in the genus Actinobacteria (Protein) and increase in the amount of Protein (*Bificobacteria* and *Collin*) in the comparison of mild to severe and moderate Covid-19 [4,22].

It was observed that the most common commensals in healthy middle-aged people were *Eubacterium*, *Faecalibacterium prausnitzii*, *Roseburia* and *Lachnospiraceae*, while in middle-aged COVID-19 patients these commensals were reduced and

conditionally-pathogenic *Clostridium hathewayi*, *Actinomyces viscosus* and *Bacteroides nordii* were increased [17,33]. Some intestinal commensals with known immunomodulatory potential, such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and bifidobacteria, were less common in COVID-19 patients [30].

In another study, Zuo et al analyzed fecal samples from 15 patients who recovered from Covid-19 disease using the sequencing method [33]. The study found that the virus persisted in the feces for a long time even after SARS-CoV-2 was eliminated [2,6], a significant increase in conditionally pathogenic bacteria and a decrease in beneficial microorganisms compared with a healthy control group. This has been suggested to be a risk factor for gastroenterologists, endoscopy staff, and for other patients during endoscopy and colonoscopy [5,6,13,30,34]. Indeed, dysfunction of the persistent intestinal microflora can lead to chronic inflammation of the gastrointestinal tract and an increase in intestinal permeability, all of which leads to disruption of the gastrointestinal tract [24].

**In conclusions** the SARS-CoV-2 virus enters the gastrointestinal tract through the fecal-oral mechanism and causes varying degrees of intestinal dysbacteriosis in almost all Covid-19 patients. An increase in the number of conditionally-pathogenic bacteria and a decrease in the amount of beneficial commensals were observed in Covid-19 disease, indicating that the clinical severity of Covid-19 disease is directly related to conditionally-pathogenic bacteria. It has been found that viral RNA can be stored for a long time in the gut of patients recovered from Covid-19 disease. In Uzbekistan, the study of the intestinal microflora of Covid-19 patients and the identification of similarities and differences from foreign data, to find ways to correct it remain relevant.

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