**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 80192

**Manuscript Type:** REVIEW

**Gastrointestinal microbiota: A predictor of COVID-19 severity?**

Neag MA *et al*. Gastrointestinal microbiota in COVID-19 pandemics

Maria Adriana Neag, Damiana-Maria Vulturar, Diana Gherman, Codrin-Constantin Burlacu, Doina Adina Todea, Anca Dana Buzoianu

**Maria Adriana Neag, Anca Dana Buzoianu,** Department of Pharmacology, Toxicology and Clinical Pharmacology, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca 400337, Romania

**Damiana-Maria Vulturar, Doina Adina Todea,** Department of Pneumology, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca 400332, Romania

**Diana Gherman,** Department of Radiology, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca 400347, Romania

**Codrin-Constantin Burlacu,** Faculty of Medicine, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca 400347, Romania

**Author contributions:** Neag MA, Vulturar DM Gherman D and Todea DA performed the research; Neag MA, Vulturar DM, Burlacu CC analyzed the data and wrote the manuscript; Burlacu CC contributed the new reagents and analytic tools; Buzoianu AD designed the research study.

**Corresponding author: Damiana-Maria Vulturar, PhD, Doctor, Researcher,** Department of Pneumology, Iuliu Hațieganu University of Medicine and Pharmacy, Victor Babes Street No. 8, Cluj-Napoca 400332, Romania. vulturar.damianamaria@elearn.umfcluj.ro

**Received:** September 19, 2022

**Revised:** October 26, 2022

**Accepted:** November 16, 2022

**Published online:** December 7, 2022

**Abstract**

Coronavirus disease 2019 (COVID-19), caused by a severe acute respiratory syndrome coronavirus 2 infection, has raised serious concerns worldwide over the past 3 years. The severity and clinical course of COVID-19 depends on many factors (*e.g.,* associated comorbidities, age, *etc*) and may have various clinical and imaging findings, which raises management concerns. Gut microbiota composition is known to influence respiratory disease, and respiratory viral infection can also influence gut microbiota. Gut and lung microbiota and their relationship (gut-lung axis) can act as modulators of inflammation. Modulating the intestinal microbiota, by improving its composition and diversity through nutraceutical agents, can have a positive impact in the prophylaxis/treatment of COVID-19.

**Key Words:** Gut microbiota; COVID-19; Prognostic biomarkers; Gut-lung axis; Probiotics; Nutraceuticals

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Neag MA, Vulturar DM, Gherman D, Burlacu CC, Todea DA, Buzoianu AD. Gastrointestinal microbiota - a predictor of COVID-19 severity? *World J Gastroenterol* 2022; 28(45): 6328-6344

**URL:** https://www.wjgnet.com/1007-9327/full/v28/i45/6328.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v28.i45.6328

**Core Tip:** In the last 10 years, the intestinal microbiota has been intensively studied in relation to various diseases from gastrointestinal to cardiovascular, respiratory, and even neurological or psychiatric diseases. Coronavirus disease 2019 (COVID-19) has been a challenge in this regard. Thus, in this review we highlighted the link between microbiota and COVID-19, aspects of the clinical and imaging manifestation and the potential role of some nutraceuticals in this widespread respiratory viral disease.

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19), first reported as a new infectious disease in December 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, can result in acute respiratory syndrome and has raised serious global concerns[1]. The clinical course of COVID-19 ranges from asymptomatic and mild to life-threatening forms[2]. Interindividual variability influences clinical symptoms and disease outcomes and is related to varying genetic profiles of the host immune response and angiotensin converting enzyme 2 (ACE2) binding affinity of SARS-CoV-2[3,4].

Disease severity and clinical course of COVID-19 depends on the patient’s associated comorbidities, including cardiovascular disease, hypertension, diabetes, chronic pulmonary disease, age, and smoking status[5]. The hyperreactivity of the host immune responses caused by SARS-CoV-2 infection, known as “cytokine storm”, leads to a massive and uncontrolled activation of proinflammatory pathways, which ultimately results in multiorgan failure and mortality[6,7]. Evolving research data suggests several conventional serum biomarkers are correlated with disease onset and disease severity, including white blood cells, D-dimers, fibrinogen, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase, serum ferritin, interleukin 6 (IL-6), alanine aminotransferase, aspartate aminotransferase (AST) and total bilirubin[8].

The human microbiota is a complex microecosystem composed of bacteria, viruses, fungi and archaea within the oral cavity, gut, lung, skin and vagina, with the highest abundance and diversity in the gut[9]. The role of microbiota in health and disease conditions has been recently shown in experimental and clinical setting[10]. The involvement of gut microbiota and its associated metabolites in maintaining body homeostasis includes regulation of host immunity, influencing physiological functions, such as digestion and nutrition and biosynthesis of vitamins and numerous active compounds[10-12]. Gut bacterial compounds play a critical role in regulating disease pathogenesis and recovery and providing promising therapeutic targets for stroke[13], neurodegenerative diseases[14], cardiovascular dysfunctions[15] and cancer-related diseases[16].

Targeting inflammatory responses triggered by SARS-CoV-2 infection by modulating the gut-lung axis represents a promising therapeutic target[17]. A clinical perspective of gut bacterial changes associated with disease severity and outcomes might provide predictive fecal and serum biomarkers with prognostic and diagnostic value[18]. Metabolomic and microbiome profiling research studies depicting bacterial changes during and after COVID-19 may provide a better understanding of the role of gut microbiota in COVID-19 pathogenesis[19,20].

This narrative review aimed to provide new insight into the involvement of gut microbiota in COVID-19 patients by modulating inflammatory responses and disease severity. For a better understanding of the translational relevance of gut microbiota as disease modifying therapy in COVID-19 disease, we summarized the most common changes in gut composition abundance of commensal and pathogenic species in relation to disease onset and severity.

**Materials and Methods**

This narrative review aimed to provide an overview of the current knowledge of the involvement of gut microbiota in COVID-19 patients. We performed an electronic search in the databases of Medline (PubMed, PubMed Central) by using different term combinations of “COVID-19” or “Sars-Cov-2” and “microbiota”, “airway microbiota”, “lung microbiota”, “gut microbiota”, “dysbiosis” and “leaky gut”.

**Short Overview of SARS-CoV-2 infection: from origins to recent data**

It is known that in the last two decades three coronaviruses have been described to cause life-threatening severe infection in humans: SARS-CoV, Middle East respiratory syndrome-CoV and SARS-CoV-2[21-23]. SARS-CoV, originated in China generated a global pandemic in 2002, having a mortality rate of 10%[21]. Middle East respiratory syndrome-CoV-2, was first reported in Saudi Arabia in 2012 and caused another transmissible disease impacting the public health sector[22]. The most recent pandemic declared was the COVID-19 pandemic, first reported in Wuhan China with a quick spread around the world[23].

The newly acquired infection is continuing to spread because of the mutations that occur in the genome and leads to an intensive viral replication with a high risk of reinfection, reducing the antibodies produced by vaccination or previous infections[24]. Being an RNA virus, SARS-CoV-2 has an important potential to adapt to new hosts, developing mutations and leading to different variants with different characteristics. To identify the new variants genomic sequencing is used. At the beginning of the pandemic, the mutation, D614G, was very contagious but not very dangerous with severe manifestations[24-26].

After this mutation, another large variety of variants have been found and named variants of concern. A variant of SARS-CoV-2 infection is a variant of concern when it impacts the public health sector. Variants of concern are linked to high transmissibility, virulence, decreased effectiveness to vaccines or medical treatment and with the capacity to evade detection.

These mutations with a high transmissibility have an increased hospital admission rate and mortality rate[27]. The five variants found to be variants of concern since the beginning of the pandemic, according to World Health Organization, are illustrated in Table 1[28]. The initial step of the infection is the recognition of the receptor, which is the key to tissue tropism[29]. The affinity of the spike glycoprotein to bind to the ACE2 receptor influences the replication and the severity of the disease[29-31].

The spike protein is formed by two subunits: The S1 subunit, which contains the receptor-binding domain and recognizes ACE2 on the host cells; and the S2 subunit, which mediates the fusion of the viral and cellular membrane. Mutations that appear in the receptor-binding domain lead to a higher viral replication and contagion. They allow the virus to not respond to vaccine-elicited antibodies[32,33]. The viral protein is cleaved by transmembrane serine protease 2, a host cell molecule involved in viral entry[34]. It has been shown that the expression of ACE2 and transmembrane serine protease 2 is increased in the nasal and oral mucosa, airways, lungs and intestine[35,36].

**Gut microbiota in health and disease**

The human gut microbiota is a complex ecosystem composed of all microorganisms (1013 to 1014) at this level, including bacteria, viruses, fungi and archaea[9]. The human microbiota, known as the “hidden organ” is composed of all the microorganisms in the oral cavity, gut, lung, skin, vagina, *etc*, but the greatest diversity and abundance is in the gut[37]. At this level, there are two dominant phyla, Firmicutes and Bacteroidetes, in healthy adults. For each of the two phyla, there are several dominant genera: *Lactobacillus, Faecalibacterium, Clostridium, Enterococcus* for Firmicutes; and *Bacteroides* and *Prevotella* for Bacteroidetes[38].

The microbiota has an important role in maintaining body homeostasis, can modulate host immunity, and has the ability to influence physiological functions[11]. Communication between the gut microbiota and the immune system is mainly carried out through mediators. Short chain fatty acids (SCFAs) are included in this category[39]. These mediators (SCFAs), represented by acetate, propionate and butyrate, play important roles through interactions with host immune cells and represent an important carbon source for colonocytes[40].

**The Involvement of gut microbiota in COVID-19 pathogenesis**

Intestinal microbiota and intestinal permeability have an important role both in regulating the transition of beneficial elements (*e.g.,* nutrients) and in stopping the penetration and transfer of harmful particles from the intestinal lumen into the circulation[41]. It has been shown that probiotics can regulate the composition of the microbiota and thus contribute to maintaining the body’s homeostasis[42]. Management of COVID-19 by administration of probiotics or other nutraceutical agents that can modulate the microbiota has not been a mainstay in the pandemic. However, the influence of COVID-19 by modulating the microbiota was not completely neglected during that period[43].

**The Gut-Lung axis in COVID-19**

Gastrointestinal symptoms account for frequent complaints of patients with SARS-CoV-2 infection[44,45]. Mounting preclinical and clinical evidence pointed out the relationship between pulmonary injury and intestinal dysfunction within viral lung infection[46], influenza A virus infection[47], bronchial asthma[48], chronic obstructive pulmonary disease[49] and cystic fibrosis[50].

Though distinguished by their functional and compositional microflora, *i.e.,* species and density, both the gut and lung microbiota systems contribute to host homeostasis by mediating local and systemic inflammatory responses, forming the so-called “gut-lung axis”[51]. Immunomodulatory effects of the gut-lung axis are mediated by mucosal-related immune systems, consisting of gut-associated lymphoid tissue and bronchial-associated lymphoid tissue[52-54].

In healthy conditions, a similar signature of microbial phyla is shared between gut and lung microbiota being provided by Firmicutes, Actinobacteria, Bacteroidetes and Proteobacteria, with Fusobacteria and Verrucomicrobia only found in the intestinal microbiota[55,56]. However, there is a distinctive pattern in the compositional bacterial genera of gut and lung microbiota, with *Lactobacillus, Clostridium, Bacillus, Enterococcus* and *Prevotella* dominant in gut microbiota and *Streptococcus, Veillonella, Fusobacterium* and *Haemophilus* dominant in lung microbiota[55,56].

The crosstalk between the gut and lung microbiota is bidirectional, with dysbiosis of either tract influencing each other[57]. Therefore, once gut microbiota are dysregulated an enrichment of blood flow with microbiota-derived products will result in a systemic inflammatory state, affecting multiple organ systems, including the lungs[58]. Several pulmonary diseases have been associated with altered samples of gut microbiota, including asthma, chronic respiratory dysfunction and pulmonary allergic responses[59,60]. However, pulmonary dysfunction during acute and chronic inflammatory lung diseases trigger intestinal changes by altering intestinal permeability and promoting bacterial translocation[61-63].

Differences in gut microbiota diversity have been reported in multiple pulmonary diseases[64]. Among 43 patients with chronic pulmonary dysfunction, an overgrowth of Proteobacteria, *i.e.,* *Haemophilus spp.*, and Firmicutes with a decreased proportion of Bacteroidetes, *i.e.,* *Prevotella spp.*, have been shown[64]. Environmental factors, such as dietary fibers, antibiotics and pre/probiotics, impacted gut microbiota, providing therapeutic insights into the microbiota-associated gut and lung dysfunction to re-establish the homeostasis in the gut-lung axis[65]. A high-fiber diet has been associated with bacterial changes in the gut-lung axis by increasing the abundance of Bacteroidaceae and decreasing the ratio of Firmicutes/Bacteroidetes in both the feces and lungs[17]. Moreover, in an experimental model of allergic lung inflammation, mice treated with a high-fiber diet or propionate showed changes in the bacterial composition of the gut and lung microbiota and an enhanced capacity of bone marrow to generate macrophage and dendritic cell precursors[17]. Moreover, in an asthma mouse model, a SCFA and fiber diet increased the phagocytic capacity of dendritic cells in the lungs and regulated T helper 2 cell-promoting inflammatory responses[17]. This experimental finding suggested that dietary fermentable fibers and SCFAs might regulate immunological tolerance in atopic asthma patients[17].

Microbiota-derived metabolites mediate the immune cross-talk between gut and lung microbiota[66,67]. SCFAs, the most dominant microbiota-derived metabolites, derived from dietary fermentable fibers in anaerobic conditions, are represented by fatty acid molecules, which are formed by chains of up to six carbon atoms, consisting of acetate, propionate or butyrate[68-70]. SCFAs play an essential role in maintaining the integrity of the intestinal epithelial barrier and mitigating inflammatory events within the gut and respiratory tract by regulating the expression of G-protein coupled receptors or histone deacetylases[68,69,71]. Circulatory acetate or propionate stimulate bone marrow hematopoiesis and enhance airway immunity by activating the differentiation of T helper cells and monocytes and increasing the expression of various chemoattractant molecules on immune cells, thereby promoting immunomodulatory mechanisms against respiratory tract infections[72,73].

The development of asthma has been shown to be influenced by the synthesis and secretion of bacterial-derived metabolites[74]. The correlation between SCFAs, specifically acetate concentration in feces, and the risk of asthma in 319 pediatric subjects demonstrated the link between dysregulation of bacterial metabolites and pulmonary dysfunction[74]. The unstable state of gut microbiota associated with an increased risk of asthma in a cohort of pediatric patients was driven by a decrease in *Faecalibacterium, Veillonella, Lachnospira* and *Rothia*[74].

Increasing experimental models ascertained the role of microbiota metabolites in immune cell differentiation. In an *in* *vivo* model of experimental colitis, butyrate promoted the differentiation of regulatory T cells and alleviated the development of colitis[67]. Butyrate enhanced IL-10 synthesis and decreased the production of IL-6 by binding GPR109a on dendritic cells and macrophages. Several expression targets were activated *via* interaction with SCFAs. For instance, in healthy conditions, butyrate could activate peroxisome proliferator-activated receptor gamma[75].

In gut microbiota analysis, Giron *et al*[76] showed that a systemic inflammatory response was linked to elevated serum markers of tight junction permeability markers and microbial translocation. Regarding the lung microbiome, Rueca *et al*[18] found the absence of *Bifidobacterium* and *Clostridium* species in the nasal/oropharyngeal samples of COVID-19 patients. An outgrowth of *Proteobacteria* and *Firmicutes* has been reported during respiratory diseases[77]. Growing clinical evidence showed an altered profile of the gut microbiome in stool samples of COVID-19 patients. A recent research study reported that changes in bacterial microbiota in COVID-19 patients could be driven by an active replication of SARS-CoV-2 within the gut[78]. In a functional analysis study of gut microbiota, a study demonstrated an increase in bacterial proliferation of *Collinsella tanakaei*, *Collinsella aerofaciens*, *Morganella morganii* and *Streptococcus infantis*, with a high metabolic rate for de novo synthesis of amino acid and nucleotides[78].

The differences in gut microbial species between diseased and healthy control patients have been correlated with disease severity and complications[20,79]. We provided a synopsis of the most common gut bacterial species changes during COVID-19 in Table 2. More studies to analyze the metabolomic and microbiome profiling data on large cohorts of COVID-19 patients to further depict the role of gut-lung axis in COVID-19 pathogenesis are needed.

**Clinical course of SARS-CoV-2 infection**

Several comorbidities associated with a higher risk of infection, such as cardiovascular disease, hypertension, diabetes, chronic pulmonary disease, age and smoking, have been reported. These factors can modulate the expression of ACE2[5]. The association between ACE2 expression and advanced age and being male are controversial[90]. Smoking led to an upregulation of ACE2 with an increased risk of severe disease[91]. Another condition that predicts severe outcomes is obesity[92]; it increased intensive care unit (ICU) admission and the requirement of invasive mechanical ventilation[93]. Also, attention should be taken in psychiatric patients (with anxiety and depression) because some possible associations between these comorbidities and sleep problems were reported[94]. Regarding the complications developed in the context of the infection, one meta-analysis showed that acute respiratory distress syndrome, shock and acute kidney injury are conditions associated with a worse prognosis and with a higher rate of ICU admission[95]. There are other complications associated with high severity like disseminated intravascular coagulation, superinfections, arrhythmias and cardiac trauma.

Several feasible circulation biomarkers used to assess disease severity included lymphocyte count, thrombocytes, serum ferritin, lactate dehydrogenase, CRP and D-dimer levels[96]. It has been shown that lymphopenia is an important and useful predictor for the severity as it was reported in those with a bad prognosis[97]. In a study of 52 critically ill COVID-19 patients, 80% reported lymphopenia[98], whereas another study of 99 patients reported a rate of only 25% in those with mild COVID-19 infection[99]. These results suggest that lymphopenia can be used as an important marker in the diagnosis of the new coronavirus infection in the evaluation of disease severity. It shows that a high number of immune cells, especially T lymphocytes, are consumed, and the immune function is inhibited[100].

In the context of COVID-19 pneumonia, a cytokine storm can be released, and the cytokines (IL-6, tumor necrosis factor-α) stimulate hepatocytes to produce CRP. It has been demonstrated that CRP is correlated with COVID-19 progression and severity[101-103]. In addition, the chronic conditions associated with hyperinflammation such as metabolic syndrome, atherosclerosis and hypertension can predict worse outcomes[104]. A study by Alamdari *et al*[105] on 459 patients with high body mass index demonstrated that high levels of CRP, lymphopenia, hypomagnesemia and creatinine at admission were associated with a higher mortality.

**High levels of serum ferritin:** High levels of serum ferritin are observed in many inflammatory diseases and is considered a biomarker in different conditions such as rheumatologic disorders or different cancers[106]. In the context of SARS-CoV-2 infection, due to the inflammatory process, the cytokines, and in particular IL-6, stimulate hepcidin production, which is involved in the regulation of ferritin[107-109].

The studies showed that high levels of ferritin were observed in COVID-19 patients *vs* controls, and those with severe or critical disease had increased levels of ferritin than those with mild or moderate disease. Moreover, it was shown that non-survivors had increased levels of serum ferritin than survivors. One meta-analysis showed that the sensitivity of serum levels of ferritin in predicting the severity of the disease is about 91% with a cutoff level of > 548.5 ng/mL[96].

**D-dimers:** D-dimers are one of the fragments produced when plasmin cleaves fibrin to break down clots. They are assessed as an algorithm in the thrombosis exclusion, but any pathologic or non-pathologic process that increases the production or disruption of fibrin can lead to high D-dimer levels[110]. Infections, venous thromboembolism and deep vein thrombosis are the most common causes of increased D-dimer levels[111].

A study by Yao *et al*[112] on 248 patients revealed that increased D-dimers at hospital admission for SARS-CoV-2 infection, after excluding pulmonary embolism and deep vein thrombosis, were associated with increased severity and with in-hospital mortality. Also, they showed a significant correlation between D-dimer levels and COVID-19 severity classified by lung involvement on computed tomography (CT) scan, oxygenation index and clinical staging according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6th edition) by the National Health Commission of China. It was highlighted that D-dimers are a useful marker to assess the severity even before the thoracic CT scan.

The hepatic injury with increased liver enzymes was reported. There are some potential mechanisms through which the liver is affected: Direct liver injury; associated inflammatory responses; congestive hepatopathy; hepatic ischemia; drug-induced liver injury; and muscle breakdown. The levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin were elevated and increased in a disease progression manner. The AST level was correlated with disease severity. According to Moon *et al*[113], AST levels had the highest correlation with mortality rate compared with other circulating markers, reflecting the involvement of liver injury in disease progression. An overview of circulating biomarkers that were correlated with COVID-19 infection is provided in Table 3.

**Diagnostic tools for THE assessment of SARS-CoV-2 infection and disease severity**

Chest imaging in the diagnosis and monitoring of COVID-19 pneumonia plays a significant role, and all available methods should be used. Chest radiography may show no abnormalities at symptom onset, with considerable findings visible only 10-12 d later[114]. Similarly, thoracic CT scans performed in the first 5 d after symptom onset may reveal isolated ground-glass opacities or consolidations in limited distribution. The full extent of the acute pulmonary manifestations increases over the 1st wk, with a peak on day 10[115]. The available imaging tools are chest radiography, chest CT and lung ultrasound (LUS).

***Chest radiography***

Chest X-ray (CXR) is commonly used as the first imaging examination when pneumonia is suspected[116]. Despite not being a substitute for real-time polymerase chain reaction test or chest CT, CXR can provide a prompt and cost-effective diagnosis in a small percentage of patients (approximately 15%)[117]. Chest radiography shows low sensitivity, as low as 25%, and high specificity, estimated at 90%, in detecting COVID-19 abnormalities, thus it should not be used as a screening method[118]. Frequent chest radiographic findings are airspace opacification, pulmonary consolidation and ground-glass opacification. Pneumonia in COVID-19 tends to be bilateral, with a pattern involving predominantly peripheral lung regions and lower lobes[1]. A proposed radiological scoring of pneumonia severity describes four disease degrees based on the percentage of lung involvement as it follows: Mild if < 25%; moderate if 25%-50%; severe 50%-75%; and critical if > 75%[119].

***Chest CT***

CT is the most sensible imaging examination and is best correlated with the severity of the disease. To reduce the patient’s exposure time to radiation, imaging tools should be performed in patients with moderate to severe symptomatology and in those with progressive alteration of respiratory parameters[120]. Frequent findings in COVID-19-positive patients are ground-glass opacities, consolidations, interlobular septal thickening and crazy paving. Additional findings consist of the reverse halo sign, air bronchogram sign, tree in bud, pleural or pericardial effusions and mediastinal lymphadenopathies. The ground-glass opacities reflect the parenchymal involvement, and they represent the most consistent feature, being found in almost all affected patients, symptomatic or asymptomatic[6]. Compared to other types of pneumonia, COVID-19 pneumonia presents with multifocal and multilobar involvement of both lungs, with a subpleural and basal distribution[121].

Disease severity can be appreciated by different scoring systems. The percentage of the overall parenchymal involvement may predict mild (< 25% lung involvement), moderate (25%-50%), severe (50%-75%) or critical (> 75%) forms of disease. Another score uses the visual estimation of the surface affected of each of the five lung lobes, with each lobe being given a score from 0 to 5, 0 meaning no involvement, 1 involving < 5%, 2 involving < 25%, 3 involving < 50%, 4 involving < 75% and 5 involving > 75% of the lobar surface. The total score obtained is the sum of the scores attributed to each lobe, and it varies from 0 to 25[122]. In a retrospective study, Bernheim *et al*[123] proposed a similar score by assessing the degree of involvement of each of the five lobes. The only difference from the previous score is that involvement of 1%-25% was attributed 1 point resulting in a score from 0 to 4 for each lobe. The total CT severity score ranged from 0 to 20. In a study of 739 patients, the authors proposed a semi-quantitative scoring system in order to predict the outcome of infected patients. They visually appreciated the pulmonary involvement by assessing each of the five lobes separately for ground-glass opacities and consolidations. Each lobe had a score varying from 0 to 7, and the maximum total score was 35[124].

Despite its high accuracy, CT may be unsuitable for critical ICU patients who may not be able to undergo transfer to the radiology department in order to perform a CT scan[120,125,126]. Moreover, there is a potentially increased risk of disease transmission to CT technicians and other patients who require imaging investigations in the same department[127]. For monitoring ICU patients, portable CXR or LUS are preferable.

***LUS***

LUS is a widely accessible, non-invasive, non-irradiating and cost-effective tool that can be used in the initial assessment and monitoring of symptomatic patients[128,129]. The main advantages of this examination reside in the possibility of being performed in children and pregnant women and at the patient’s bedside. It is portable and offers replicable examination for follow-up[130,131]. Portable ultrasound devices can be used in ICU departments, both by radiologists and clinicians, offering real-time information about a patient’s evolution.

Numerous authors stated that LUS can offer similar diagnostic information to chest CT in the evaluation of COVID-19 pneumonia[126,132,133]. Gibbons *et al*[132] concluded that LUS compared to portable CXR had a higher sensitivity for detection of viral pneumonia. LUS findings in COVID-19 patients include multiple B lines below the pleural surface, subpleural consolidations, pleural thickening and irregularity[134]. The B lines depict the interstitial involvement and represent the most common ultrasonographic pattern found in patients with COVID-19[129,132,135]. Despite having a high sensitivity in detecting COVID-19 pneumonia in subpleural lung regions, the deep pulmonary parenchyma remains inaccessible to LUS due to air interposition leading to an underestimation of the disease extent[136]. LUS findings are not distinctive for viral cases of pneumonia, but just as it was previously discussed in the case of chest radiography and chest CT scans, the bilateral and predominantly basal distribution is a strong indicator for COVID-19 pneumonia rather than influenza or bacterial pneumonia[137]. Nonetheless, LUS has a low specificity, since it cannot distinguish from other pulmonary and cardiac conditions such as acute respiratory distress syndrome, heart failure and subpleural lung masses[125,136].

**Translational relevance of Gut microbiota in modifying disease severity and outcomes of COVID-19 patients**

The involvement of gut microbiota in modifying disease outcomes and therapeutic responses of COVID-19 patients might represent a promising therapeutic strategy. Emerging clinical studies suggested that dysfunctional immune response triggered by gut microbiota dysregulation upon SARS-CoV-2 infection might influence the severity and the course of COVID-19[20,138].

The proinflammatory state triggered by the host immune response against SARS-CoV-2 infection promotes changes in gut commensal microflora, leading to dysbiosis, which will further result in alteration of the intestinal epithelial barrier[51,138,139]. Once the integrity of the intestinal barrier is disrupted, the high permeable state of the intestine creates the most favorable conditions for entering into the circulation of bacterial products and toxins, activating a systemic inflammatory response[140].

Evolving data examined predictive biomarkers of disease severity from serum samples of COVID-19 patients, which were correlated with inflammatory response and disease severity[20,138]. Compared to controls, the serum samples of COVID-19 patients exhibited high levels of fatty acid-binding protein 2, peptidoglycan and lipopolysaccharide, markers of gut permeability, suggesting the unstable state of the intestinal barrier within these patients[138].

Significant dysbiosis in 146 COVID-19 patients has been reported by Prasad *et al*[138]. The phylogenetic changes in the serum microbiome of COVID-19 patients consisted of enrichment of *Actinobacteria spp.* and underrepresentation of *Bacteroides spp.,* with an increased ratio of Firmicutes to Bacteroidetes[138]. Therefore, the unstable state of gut microbiota in COVID-19 patients is reflected by a decrease in beneficial bacteria, *i.e.,* *Bifidobacterium*, and an increase in deleterious bacteria related to bacteremia or sepsis, *i.e.,* *Brevibacterium* and *Pantoea*[138].

By RNA and DNA sequencing of blood and stool samples of COVID-19 patients, Yeoh *et al*[20] depicted a distinct signature of gut microbiota composition in 100 positive subjects. A decreased abundance of gut commensals such as *Faecalibacterium prausnitzii*, *Eubacterium rectale* and *Bifidobacterial* have been reported up to 30 d after disease course in 87 hospitalized COVID-19 patients, suggesting the long-term dysregulation of gut microbiota[20].

At the species level, the authors identified a significant association between the compositional abundance of gut microbiota and disease severity. The microbial species, *Faecalibacterium prausnitzii*, *Bifidobacterium bifidum*, *Bifidobacterial adolescentis* and *Eubacterium rectale* negatively correlated with disease severity, the mean value of the gut microbial composition decreased compared to non-COVID-19, and mild COVID-19 samples correlated to the lowest value compared to the severe and critical patients[20].

Analysis of gut microbial samples might provide valuable prognostic serum markers, which could predict disease severity and outcomes[20]. Correlational analysis between different microbial taxa and cytokine and chemokine levels suggested the role of gut microbiota in regulating the magnitude of immune response and modifying disease severity of COVID-19 disease[20].

Thus, the decrease in the abundance of *Bifidobacterium adolescentis, Faecalibacterium prausnitzii* and *Eubacterium rectale* in COVID-19 patients was associated with elevated cytokine levels of tumor necrosis factor-α, IL-10, C-C motif chemokine ligand 2 and CXCL10[20]. In identifying the microbial species associated with disease severity, [Schult](https://www.tandfonline.com/author/Schult%2C+David) *et al*[79] analyzed gut microbial profiles and observed a different bacterial composition in COVID-19 patients with a low risk of complications, with a predominance of *Faecalibacterium* *prausznitzii*, and high risk complications, in which *Parabacteroides spp.* Dominates. The changes in the abundance of microbial species were more pronounced in patients with severe associated conditions, such as acute kidney injury and acute respiratory distress syndrome, followed by a lesser microbiota change in acute cardiac events and venous thromboembolism. Moreover, the authors proposed 12 gut microbial species as cocktail biomarkers with an accuracy of 0.94 for predicting the progression of disease and the severity of COVID-19 patients[79]. Thus, the abundance of *Ruthenibacterium lactatiformans*, *Clostridium innocuum* and *Alistipes finegoldii* was correlated with inflammatory blood markers, such as white blood cells, CRP and procalcitonin, and disease progression. In severe and fatal cases, the microbial profile of the gut exhibited depleted levels of *Blautia luti*, *Faecalibacterium prausnitzii*, *Alistipes putredinis*, *Dorea longicatena* and *Gemmiger formicilis*[79].

Aging, diet and comorbidities, such as obesity, diabetes and cardiovascular diseases, have a significant impact on the microbial profile of the gut, leading to dysbiosis[141-144]. Age and comorbidity-related changes in the gut microbial profile of COVID-19 patients influence immune regulatory mechanisms, which might explain the severe forms of disease and the associated complications in older and comorbid patients[145].

In relation to the mechanistic data mentioned, patients with severe forms of COVID-19 faced more pronounced gastrointestinal symptoms, suggesting the association between clinical symptoms and disrupted gut microbiota during COVID-19 disease[146,147]. Another study revealed a depressed state of bacterial composition species, consisting of lower levels of beneficial symbionts and higher levels of opportunistic pathogens, such as *Streptococcus*, *Rothia*, *Actinomyces* and *Veillonella*[80]. The authors proposed five gut microflora biomarkers, including *Intestinibacter*, *Erysipelatoclostridium*, *Actinomyces*, *Fusicatenibacter* and *Romboutsia* with diagnostic value to distinguish between COVID-19 patients and healthy controls[80].

The long-term dysregulated effects of SARS-CoV-2 have been revealed in fecal samples of COVID-19 patients, with persisted gut dysbiosis after clearance of the virus[148]. Prognostic valuable bacterial-based markers include *Coprobacillus*, *Clostridium ramosum* and *Clostridium hathewayi*, which were associated with COVID-19 severity. In a murine gut model, some beneficial bacterial species, including *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis* and *Bacteroides ovatus*, downregulate ACE2 expression level, negatively correlating with the viral load of SARS-CoV-2[148].

At the basis of immune interactions between lung and gut microbiota are microbiota-derived metabolites that modulate host immune cells in a direct or indirect manner[66,149]. Some bacteria species, such as *Anaerostipes butyraticus*, *Faecalibacterium prausnitzii* and *Roseburia intestinalis*, display enzymatic systems to digest the complex carbohydrates, which resulted in SCFA products[70,150]. By analyzing oral microbiota, Firmicutes, Actinobacteria and Bacteroidetes were enriched in the COVID-19 group compared with healthy controls. Moreover, the oral microbiota exhibited fewer levels of butyric acid-producing bacteria and more lipopolysaccharide-producing bacteria in the positive patients[77].

Changes in the metabolomic profile of fecal samples of COVID-19 patients have been correlated with different microbial composition profiles[19]. A better understanding of metabolic changes in serum or fecal COVID-19 samples will further provide new insight into the gut-lung axis and propose putative prognostic markers in COVID-19. Up to 20 metabolites were changed in the fecal sample of COVID-19 patients, including monosaccharides, *i.e.,* D-allose, D-glucose and D-arabinose, nucleotides, *i.e.,* hypoxanthine, pseudouridine and inosine, and amino acids, *i.e.,* l-tyrosine and l-tryptophan, and were associated with bacterial species modifications[19].

Targeting severe immune responses in COVID-19 represents the main therapeutic approach[151]. Recent studies pointed out the role of a high-fiber diet and probiotics as disease-modifying therapy in COVID-19[151,152]. The role of nutraceutical compounds, consisting of vitamins, dietary supplements and pro/prebiotics in COVID-19, have been reported to improve the clinical course and severity of COVID-19 disease (Table 4). Several clinical trials investigating the role of probiotics enriched with different types of beneficial species are in progress (NCT04854941, NCT05080244, NCT04390477).

**CONCLUSION**

There is evidence that changes in gut microbiota are an important factor in the pathogenesis of COVID-19. An important role in this disease is also played by the relationship between the gut and the lungs, known as the “gut-lung axis”. Modulating gut microbiota to increase diversity and abundance can positively influence the severity of COVID-19. Further studies are needed to explore the microbiota in COVID-19 patients with varying degrees of severity, in post-COVID-19 patients and their medical history with nutraceutical agents.

**REFERENCES**

1 **Nugraha RV**, Ridwansyah H, Ghozali M, Khairani AF, Atik N. Traditional Herbal Medicine Candidates as Complementary Treatments for COVID-19: A Review of Their Mechanisms, Pros and Cons. *Evid Based Complement Alternat Med* 2020; **2020**: 2560645 [PMID: 33101440 DOI: 10.1155/2020/2560645]

2 **Yuen KS**, Ye ZW, Fung SY, Chan CP, Jin DY. SARS-CoV-2 and COVID-19: The most important research questions. *Cell Biosci* 2020; **10**: 40 [PMID: 32190290 DOI: 10.1186/s13578-020-00404-4]

3 **Vadgama N**, Kreymerman A, Campbell J, Shamardina O, Brugger C, Research Consortium GE, Deaconescu AM, Lee RT, Penkett CJ, Gifford CA, Mercola M, Nasir J, Karakikes I. SARS-CoV-2 Susceptibility and *ACE2* Gene Variations Within Diverse Ethnic Backgrounds. *Front Genet* 2022; **13**: 888025 [PMID: 35571054 DOI: 10.3389/fgene.2022.888025]

4 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

5 **Jackson CB**, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* 2022; **23**: 3-20 [PMID: 34611326 DOI: 10.1038/s41580-021-00418-x]

6 **Ragab D**, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. *Front Immunol* 2020; **11**: 1446 [PMID: 32612617 DOI: 10.3389/fimmu.2020.01446]

7 **Sinha P**, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? *JAMA Intern Med* 2020; **180**: 1152-1154 [PMID: 32602883 DOI: 10.1001/jamainternmed.2020.3313]

8 **Kermali M**, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci* 2020; **254**: 117788 [PMID: 32475810 DOI: 10.1016/j.lfs.2020.117788]

9 **Gill SR**, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JI, Relman DA, Fraser-Liggett CM, Nelson KE. Metagenomic analysis of the human distal gut microbiome. *Science* 2006; **312**: 1355-1359 [PMID: 16741115 DOI: 10.1126/science.1124234]

10 **Shreiner AB**, Kao JY, Young VB. The gut microbiome in health and in disease. *Curr Opin Gastroenterol* 2015; **31**: 69-75 [PMID: 25394236 DOI: 10.1097/MOG.0000000000000139]

11 **Honda K**, Littman DR. The microbiota in adaptive immune homeostasis and disease. *Nature* 2016; **535**: 75-84 [PMID: 27383982 DOI: 10.1038/nature18848]

12 **Cabrera-Mulero A**, Tinahones A, Bandera B, Moreno-Indias I, Macías-González M, Tinahones FJ. Keto microbiota: A powerful contributor to host disease recovery. *Rev Endocr Metab Disord* 2019; **20**: 415-425 [PMID: 31720986 DOI: 10.1007/s11154-019-09518-8]

13 **Battaglini D**, Pimentel-Coelho PM, Robba C, Dos Santos CC, Cruz FF, Pelosi P, Rocco PRM. Gut Microbiota in Acute Ischemic Stroke: From Pathophysiology to Therapeutic Implications. *Front Neurol* 2020; **11**: 598 [PMID: 32670191 DOI: 10.3389/fneur.2020.00598]

14 **Zhang H**, Chen Y, Wang Z, Xie G, Liu M, Yuan B, Chai H, Wang W, Cheng P. Implications of Gut Microbiota in Neurodegenerative Diseases. *Front Immunol* 2022; **13**: 785644 [PMID: 35237258 DOI: 10.3389/fimmu.2022.785644]

15 **Zhou W**, Cheng Y, Zhu P, Nasser MI, Zhang X, Zhao M. Implication of Gut Microbiota in Cardiovascular Diseases. *Oxid Med Cell Longev* 2020; **2020**: 5394096 [PMID: 33062141 DOI: 10.1155/2020/5394096]

16 **Akbar N**, Khan NA, Muhammad JS, Siddiqui R. The role of gut microbiome in cancer genesis and cancer prevention. *Health Sci Rev* 2022; **2**: 100010 [DOI: 10.1016/j.hsr.2021.100010]

17 **Trompette A**, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, Blanchard C, Junt T, Nicod LP, Harris NL, Marsland BJ. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med* 2014; **20**: 159-166 [PMID: 24390308 DOI: 10.1038/nm.3444]

18 **Rueca M**, Fontana A, Bartolini B, Piselli P, Mazzarelli A, Copetti M, Binda E, Perri F, Gruber CEM, Nicastri E, Marchioni L, Ippolito G, Capobianchi MR, Di Caro A, Pazienza V. Investigation of Nasal/Oropharyngeal Microbial Community of COVID-19 Patients by 16S rDNA Sequencing. *Int J Environ Res Public Health* 2021; **18** [PMID: 33672177 DOI: 10.3390/ijerph18042174]

19 **Lv L**, Jiang H, Chen Y, Gu S, Xia J, Zhang H, Lu Y, Yan R, Li L. The faecal metabolome in COVID-19 patients is altered and associated with clinical features and gut microbes. *Anal Chim Acta* 2021; **1152**: 338267 [PMID: 33648648 DOI: 10.1016/j.aca.2021.338267]

20 **Yeoh YK**, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, Chung AC, Cheung CP, Tso EY, Fung KS, Chan V, Ling L, Joynt G, Hui DS, Chow KM, Ng SSS, Li TC, Ng RW, Yip TC, Wong GL, Chan FK, Wong CK, Chan PK, Ng SC. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021; **70**: 698-706 [PMID: 33431578 DOI: 10.1136/gutjnl-2020-323020]

21 **Drosten C**, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA, Berger A, Burguière AM, Cinatl J, Eickmann M, Escriou N, Grywna K, Kramme S, Manuguerra JC, Müller S, Rickerts V, Stürmer M, Vieth S, Klenk HD, Osterhaus AD, Schmitz H, Doerr HW. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; **348**: 1967-1976 [PMID: 12690091 DOI: 10.1056/NEJMoa030747]

22 **Zaki AM**, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367**: 1814-1820 [PMID: 23075143 DOI: 10.1056/NEJMoa1211721]

23 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

24 **Akkız H**. The Biological Functions and Clinical Significance of SARS-CoV-2 Variants of Corcern. *Front Med (Lausanne)* 2022; **9**: 849217 [PMID: 35669924 DOI: 10.3389/fmed.2022.849217]

25 **Korber B**, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, Hengartner N, Giorgi EE, Bhattacharya T, Foley B, Hastie KM, Parker MD, Partridge DG, Evans CM, Freeman TM, de Silva TI; Sheffield COVID-19 Genomics Group, McDanal C, Perez LG, Tang H, Moon-Walker A, Whelan SP, LaBranche CC, Saphire EO, Montefiori DC. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. *Cell* 2020; **182**: 812-827.e19 [PMID: 32697968 DOI: 10.1016/j.cell.2020.06.043]

26 **Aleem A**, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). 2022 Oct 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 34033342]

27 **Davies NG**, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, Pearson CAB, Russell TW, Tully DC, Washburne AD, Wenseleers T, Gimma A, Waites W, Wong KLM, van Zandvoort K, Silverman JD; CMMID COVID-19 Working Group; COVID-19 Genomics UK (COG-UK) Consortium, Diaz-Ordaz K, Keogh R, Eggo RM, Funk S, Jit M, Atkins KE, Edmunds WJ. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science* 2021; **372** [PMID: 33658326 DOI: 10.1126/science.abg3055]

28 **World Health Organization**. Tracking SARS-CoV-2 variants. [cited 22 February 2022]. Available from: https://www.who.int/activities/tracking-SARS-CoV-2-variants

29 **V'kovski P**, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol* 2021; **19**: 155-170 [PMID: 33116300 DOI: 10.1038/s41579-020-00468-6]

30 **Harvey WT**, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, Ludden C, Reeve R, Rambaut A; COVID-19 Genomics UK (COG-UK) Consortium, Peacock SJ, Robertson DL. SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol* 2021; **19**: 409-424 [PMID: 34075212 DOI: 10.1038/s41579-021-00573-0]

31 **Scudellari M**. How the coronavirus infects cells - and why Delta is so dangerous. *Nature* 2021; **595**: 640-644 [PMID: 34321669 DOI: 10.1038/d41586-021-02039-y]

32 **Nagesha** **SN**, Ramesh BN, Pradeep C, Shashidhara KS, Ramakrishnappa T, Krishnaprasad BT, Jnanashree SM, Manohar M, Arunkumar N, Yallappa, Dhanush Patel D, Rakesh TV, Girish E, Bagoji M, Chandaragi SS. SARS-CoV 2 spike protein S1 subunit as an ideal target for stable vaccines: A bioinformatic study. *Mater Today Proc* 2022; **49**: 904-912 [PMID: 34307057 DOI: 10.1016/j.matpr.2021.07.163]

33 **Walls AC**, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**: 281-292.e6 [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058]

34 **Mollica V**, Rizzo A, Massari F. The pivotal role of TMPRSS2 in coronavirus disease 2019 and prostate cancer. *Future Oncol* 2020; **16**: 2029-2033 [PMID: 32658591 DOI: 10.2217/fon-2020-0571]

35 **Akkiz H**. Implications of the Novel Mutations in the SARS-CoV-2 Genome for Transmission, Disease Severity, and the Vaccine Development. *Front Med (Lausanne)* 2021; **8**: 636532 [PMID: 34026780 DOI: 10.3389/fmed.2021.636532]

36 **Lamers MM**, Beumer J, van der Vaart J, Knoops K, Puschhof J, Breugem TI, Ravelli RBG, Paul van Schayck J, Mykytyn AZ, Duimel HQ, van Donselaar E, Riesebosch S, Kuijpers HJH, Schipper D, van de Wetering WJ, de Graaf M, Koopmans M, Cuppen E, Peters PJ, Haagmans BL, Clevers H. SARS-CoV-2 productively infects human gut enterocytes. *Science* 2020; **369**: 50-54 [PMID: 32358202 DOI: 10.1126/science.abc1669]

37 **Hou K**, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J, Chen ZS. Microbiota in health and diseases. *Signal Transduct Target Ther* 2022; **7**: 135 [PMID: 35461318 DOI: 10.1038/s41392-022-00974-4]

38 **Senghor B**, Sokhna C, Ruimy R, Lagier JC. Gut microbiota diversity according to dietary habits and geographical provenance. *Hum Microbiome J* 2018 [DOI: 10.1016/j.humic.2018.01.001]

39 **Spencer SP**, Fragiadakis GK, Sonnenburg JL. Pursuing Human-Relevant Gut Microbiota-Immune Interactions. *Immunity* 2019; **51**: 225-239 [PMID: 31433970 DOI: 10.1016/j.immuni.2019.08.002]

40 **Martin-Gallausiaux C**, Marinelli L, Blottière HM, Larraufie P, Lapaque N. SCFA: mechanisms and functional importance in the gut. *Proc Nutr Soc* 2021; **80**: 37-49 [PMID: 32238208 DOI: 10.1017/S0029665120006916]

41 **Zhao S**, Feng P, Meng W, Jin W, Li X, Li X. Modulated Gut Microbiota for Potential COVID-19 Prevention and Treatment. *Front Med (Lausanne)* 2022; **9**: 811176 [PMID: 35308540 DOI: 10.3389/fmed.2022.811176]

42 **Liang Y**, Liang S, Zhang Y, Deng Y, He Y, Chen Y, Liu C, Lin C, Yang Q. Oral Administration of Compound Probiotics Ameliorates HFD-Induced Gut Microbe Dysbiosis and Chronic Metabolic Inflammation via the G Protein-Coupled Receptor 43 in Non-alcoholic Fatty Liver Disease Rats. *Probiotics Antimicrob Proteins* 2019; **11**: 175-185 [PMID: 29353414 DOI: 10.1007/s12602-017-9378-3]

43 **Khan AA**, Singh H, Bilal M, Ashraf MT. Microbiota, probiotics and respiratory infections: the three musketeers can tip off potential management of COVID-19. *Am J Transl Res* 2021; **13**: 10977-10993 [PMID: 34786037]

44 **Marasco G**, Cremon C, Barbaro MR, Salvi D, Cacciari G, Kagramanova A, Bordin D, Drug V, Miftode E, Fusaroli P, Mohamed SY, Ricci C, Bellini M, Rahman MM, Melcarne L, Santos J, Lobo B, Bor S, Yapali S, Akyol D, Sapmaz FP, Urun YY, Eskazan T, Celebi A, Kacmaz H, Ebik B, Binicier HC, Bugdayci MS, Yağcı MB, Pullukcu H, Kaya BY, Tureyen A, Hatemi İ, Koc ES, Sirin G, Calıskan AR, Bengi G, Alıs EE, Lukic S, Trajkovska M, Hod K, Dumitrascu D, Pietrangelo A, Corradini E, Simren M, Sjolund J, Tornkvist N, Ghoshal UC, Kolokolnikova O, Colecchia A, Serra J, Maconi G, De Giorgio R, Danese S, Portincasa P, Di Stefano M, Maggio M, Philippou E, Lee YY, Venturi A, Borghi C, Zoli M, Gionchetti P, Viale P, Stanghellini V, Barbara G; GI-COVID19 Study Group. Prevalence of Gastrointestinal Symptoms in Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Results of the Prospective Controlled Multinational GI-COVID-19 Study. *Am J Gastroenterol* 2022; **117**: 147-157 [PMID: 34751672 DOI: 10.14309/ajg.0000000000001541]

45 **Minodier L**, Charrel RN, Ceccaldi PE, van der Werf S, Blanchon T, Hanslik T, Falchi A. Prevalence of gastrointestinal symptoms in patients with influenza, clinical significance, and pathophysiology of human influenza viruses in faecal samples: what do we know? *Virol J* 2015; **12**: 215 [PMID: 26651485 DOI: 10.1186/s12985-015-0448-4]

46 **Groves HT**, Cuthbertson L, James P, Moffatt MF, Cox MJ, Tregoning JS. Respiratory Disease following Viral Lung Infection Alters the Murine Gut Microbiota. *Front Immunol* 2018; **9**: 182 [PMID: 29483910 DOI: 10.3389/fimmu.2018.00182]

47 **Yildiz S**, Mazel-Sanchez B, Kandasamy M, Manicassamy B, Schmolke M. Influenza A virus infection impacts systemic microbiota dynamics and causes quantitative enteric dysbiosis. *Microbiome* 2018; **6**: 9 [PMID: 29321057 DOI: 10.1186/s40168-017-0386-z]

48 **Roussos A**, Koursarakos P, Patsopoulos D, Gerogianni I, Philippou N. Increased prevalence of irritable bowel syndrome in patients with bronchial asthma. *Respir Med* 2003; **97**: 75-79 [PMID: 12556015 DOI: 10.1053/rmed.2001.1409]

49 **Keely S**, Hansbro PM. Lung-gut cross talk: a potential mechanism for intestinal dysfunction in patients with COPD. *Chest* 2014; **145**: 199-200 [PMID: 24493496 DOI: 10.1378/chest.13-2077]

50 **Baral V**, Connett G. Acute intestinal obstruction as a presentation of cystic fibrosis in infancy. *J Cyst Fibros* 2008; **7**: 277-279 [PMID: 18053778 DOI: 10.1016/j.jcf.2007.10.005]

51 **Budden KF**, Gellatly SL, Wood DL, Cooper MA, Morrison M, Hugenholtz P, Hansbro PM. Emerging pathogenic links between microbiota and the gut-lung axis. *Nat Rev Microbiol* 2017; **15**: 55-63 [PMID: 27694885 DOI: 10.1038/nrmicro.2016.142]

52 **Heier I**, Malmström K, Sajantila A, Lohi J, Mäkelä M, Jahnsen FL. Characterisation of bronchus-associated lymphoid tissue and antigen-presenting cells in central airway mucosa of children. *Thorax* 2011; **66**: 151-156 [PMID: 21163807 DOI: 10.1136/thx.2010.149591]

53 **Compare D**, Coccoli P, Rocco A, Nardone OM, De Maria S, Cartenì M, Nardone G. Gut--liver axis: the impact of gut microbiota on non alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis* 2012; **22**: 471-476 [PMID: 22546554 DOI: 10.1016/j.numecd.2012.02.007]

54 **Neag MA**, Mitre AO, Catinean A, Buzoianu AD. Overview of the microbiota in the gut-liver axis in viral B and C hepatitis. *World J Gastroenterol* 2021; **27**: 7446-7461 [PMID: 34887642 DOI: 10.3748/wjg.v27.i43.7446]

55 **Rinninella E**, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, Mele MC. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms* 2019; **7** [PMID: 30634578 DOI: 10.3390/microorganisms7010014]

56 **Shah T**, Shah Z, Baloch Z, Cui X. The role of microbiota in respiratory health and diseases, particularly in tuberculosis. *Biomed Pharmacother* 2021; **143**: 112108 [PMID: 34560539 DOI: 10.1016/j.biopha.2021.112108]

57 **Kraft SC**, Earle RH, Roesler M, Esterly JR. Unexplained bronchopulmonary disease with inflammatory bowel disease. *Arch Intern Med* 1976; **136**: 454-459 [PMID: 1267553]

58 **Sze MA**, Tsuruta M, Yang SW, Oh Y, Man SF, Hogg JC, Sin DD. Changes in the bacterial microbiota in gut, blood, and lungs following acute LPS instillation into mice lungs. *PLoS One* 2014; **9**: e111228 [PMID: 25333938 DOI: 10.1371/journal.pone.0111228]

59 **Enaud R**, Prevel R, Ciarlo E, Beaufils F, Wieërs G, Guery B, Delhaes L. The Gut-Lung Axis in Health and Respiratory Diseases: A Place for Inter-Organ and Inter-Kingdom Crosstalks. *Front Cell Infect Microbiol* 2020; **10**: 9 [PMID: 32140452 DOI: 10.3389/fcimb.2020.00009]

60 **Marsland BJ**, Trompette A, Gollwitzer ES. The Gut-Lung Axis in Respiratory Disease. *Ann Am Thorac Soc* 2015; **12** Suppl 2: S150-S156 [PMID: 26595731 DOI: 10.1513/AnnalsATS.201503-133AW]

61 **Dickson RP**, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, Huffnagle GB. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. *Nat Microbiol* 2016; **1**: 16113 [PMID: 27670109 DOI: 10.1038/nmicrobiol.2016.113]

62 **Abrahamsson TR**, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy* 2014; **44**: 842-850 [PMID: 24330256 DOI: 10.1111/cea.12253]

63 **Bruzzese E**, Callegari ML, Raia V, Viscovo S, Scotto R, Ferrari S, Morelli L, Buccigrossi V, Lo Vecchio A, Ruberto E, Guarino A. Disrupted intestinal microbiota and intestinal inflammation in children with cystic fibrosis and its restoration with Lactobacillus GG: a randomised clinical trial. *PLoS One* 2014; **9**: e87796 [PMID: 24586292 DOI: 10.1371/journal.pone.0087796]

64 **Hilty M**, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, Davies J, Ervine A, Poulter L, Pachter L, Moffatt MF, Cookson WO. Disordered microbial communities in asthmatic airways. *PLoS One* 2010; **5**: e8578 [PMID: 20052417 DOI: 10.1371/journal.pone.0008578]

65 **Anand S**, Mande SS. Diet, Microbiota and Gut-Lung Connection. *Front Microbiol* 2018; **9**: 2147 [PMID: 30283410 DOI: 10.3389/fmicb.2018.02147]

66 **Yoo JY**, Groer M, Dutra SVO, Sarkar A, McSkimming DI. Gut Microbiota and Immune System Interactions. *Microorganisms* 2020; **8** [PMID: 33076307 DOI: 10.3390/microorganisms8101587]

67 **Furusawa Y**, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013; **504**: 446-450 [PMID: 24226770 DOI: 10.1038/nature12721]

68 **Kau AL**, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. *Nature* 2011; **474**: 327-336 [PMID: 21677749 DOI: 10.1038/nature10213]

69 **Zhao L**, Zhang F, Ding X, Wu G, Lam YY, Wang X, Fu H, Xue X, Lu C, Ma J, Yu L, Xu C, Ren Z, Xu Y, Xu S, Shen H, Zhu X, Shi Y, Shen Q, Dong W, Liu R, Ling Y, Zeng Y, Wang X, Zhang Q, Wang J, Wang L, Wu Y, Zeng B, Wei H, Zhang M, Peng Y, Zhang C. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science* 2018; **359**: 1151-1156 [PMID: 29590046 DOI: 10.1126/science.aao5774]

70 **Parada Venegas D**, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol* 2019; **10**: 277 [PMID: 30915065 DOI: 10.3389/fimmu.2019.00277]

71 **Husted AS**, Trauelsen M, Rudenko O, Hjorth SA, Schwartz TW. GPCR-Mediated Signaling of Metabolites. *Cell Metab* 2017; **25**: 777-796 [PMID: 28380372 DOI: 10.1016/j.cmet.2017.03.008]

72 **Landsman L**, Jung S. Lung macrophages serve as obligatory intermediate between blood monocytes and alveolar macrophages. *J Immunol* 2007; **179**: 3488-3494 [PMID: 17785782 DOI: 10.4049/jimmunol.179.6.3488]

73 **Landsman L**, Varol C, Jung S. Distinct differentiation potential of blood monocyte subsets in the lung. *J Immunol* 2007; **178**: 2000-2007 [PMID: 17277103 DOI: 10.4049/jimmunol.178.4.2000]

74 **Arrieta MC**, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, Kuzeljevic B, Gold MJ, Britton HM, Lefebvre DL, Subbarao P, Mandhane P, Becker A, McNagny KM, Sears MR, Kollmann T; CHILD Study Investigators, Mohn WW, Turvey SE, Finlay BB. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015; **7**: 307ra152 [PMID: 26424567 DOI: 10.1126/scitranslmed.aab2271]

75 **Martin-Gallausiaux C**, Béguet-Crespel F, Marinelli L, Jamet A, Ledue F, Blottière HM, Lapaque N. Butyrate produced by gut commensal bacteria activates TGF-beta1 expression through the transcription factor SP1 in human intestinal epithelial cells. *Sci Rep* 2018; **8**: 9742 [PMID: 29950699 DOI: 10.1038/s41598-018-28048-y]

76 **Giron LB**, Dweep H, Yin X, Wang H, Damra M, Goldman AR, Gorman N, Palmer CS, Tang HY, Shaikh MW, Forsyth CB, Balk RA, Zilberstein NF, Liu Q, Kossenkov A, Keshavarzian A, Landay A, Abdel-Mohsen M. Corrigendum: Plasma Markers of Disrupted Gut Permeability in Severe COVID-19 Patients. *Front Immunol* 2021; **12**: 779064 [PMID: 34671365 DOI: 10.3389/fimmu.2021.779064]

77 **Ren Z**, Wang H, Cui G, Lu H, Wang L, Luo H, Chen X, Ren H, Sun R, Liu W, Liu X, Liu C, Li A, Wang X, Rao B, Yuan C, Zhang H, Sun J, Chen X, Li B, Hu C, Wu Z, Yu Z, Kan Q, Li L. Alterations in the human oral and gut microbiomes and lipidomics in COVID-19. *Gut* 2021; **70**: 1253-1265 [PMID: 33789966 DOI: 10.1136/gutjnl-2020-323826]

78 **Zuo T**, Liu Q, Zhang F, Lui GC, Tso EY, Yeoh YK, Chen Z, Boon SS, Chan FK, Chan PK, Ng SC. Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. *Gut* 2021; **70**: 276-284 [PMID: 32690600 DOI: 10.1136/gutjnl-2020-322294]

79 **Schult D**, Reitmeier S, Koyumdzhieva P, Lahmer T, Middelhoff M, Erber J, Schneider J, Kager J, Frolova M, Horstmann J, Fricke L, Steiger K, Jesinghaus M, Janssen KP, Protzer U, Neuhaus K, Schmid RM, Haller D, Quante M. Gut bacterial dysbiosis and instability is associated with the onset of complications and mortality in COVID-19. *Gut Microbes* 2022; **14**: 2031840 [PMID: 35174781 DOI: 10.1080/19490976.2022.2031840]

80 **Gu S**, Chen Y, Wu Z, Chen Y, Gao H, Lv L, Guo F, Zhang X, Luo R, Huang C, Lu H, Zheng B, Zhang J, Yan R, Zhang H, Jiang H, Xu Q, Guo J, Gong Y, Tang L, Li L. Alterations of the Gut Microbiota in Patients With Coronavirus Disease 2019 or H1N1 Influenza. *Clin Infect Dis* 2020; **71**: 2669-2678 [PMID: 32497191 DOI: 10.1093/cid/ciaa709]

81 **Wu Y**, Cheng X, Jiang G, Tang H, Ming S, Tang L, Lu J, Guo C, Shan H, Huang X. Altered oral and gut microbiota and its association with SARS-CoV-2 viral load in COVID-19 patients during hospitalization. *NPJ Biofilms Microbiomes* 2021; **7**: 61 [PMID: 34294722 DOI: 10.1038/s41522-021-00232-5]

82 **Mizutani T**, Ishizaka A, Koga M, Ikeuchi K, Saito M, Adachi E, Yamayoshi S, Iwatsuki-Horimoto K, Yasuhara A, Kiyono H, Matano T, Suzuki Y, Tsutsumi T, Kawaoka Y, Yotsuyanagi H. Correlation Analysis between Gut Microbiota Alterations and the Cytokine Response in Patients with Coronavirus Disease during Hospitalization. *Microbiol Spectr* 2022; **10**: e0168921 [PMID: 35254122 DOI: 10.1128/spectrum.01689-21]

83 **Newsome RC**, Gauthier J, Hernandez MC, Abraham GE, Robinson TO, Williams HB, Sloan M, Owings A, Laird H, Christian T, Pride Y, Wilson KJ, Hasan M, Parker A, Senitko M, Glover SC, Gharaibeh RZ, Jobin C. The gut microbiome of COVID-19 recovered patients returns to uninfected status in a minority-dominated United States cohort. *Gut Microbes* 2021; **13**: 1-15 [PMID: 34100340 DOI: 10.1080/19490976.2021.1926840]

84 **Tao W**, Zhang G, Wang X, Guo M, Zeng W, Xu Z, Cao D, Pan A, Wang Y, Zhang K, Ma X, Chen Z, Jin T, Liu L, Weng J, Zhu S. Analysis of the intestinal microbiota in COVID-19 patients and its correlation with the inflammatory factor IL-18. *Med Microecol* 2020; **5**: 100023 [PMID: 34173452 DOI: 10.1016/j.medmic.2020.100023]

85 **Hernández-Terán A**, Mejía-Nepomuceno F, Herrera MT, Barreto O, García E, Castillejos M, Boukadida C, Matias-Florentino M, Rincón-Rubio A, Avila-Rios S, Mújica-Sánchez M, Serna-Muñoz R, Becerril-Vargas E, Guadarrama-Pérez C, Ahumada-Topete VH, Rodríguez-Llamazares S, Martínez-Orozco JA, Salas-Hernández J, Pérez-Padilla R, Vázquez-Pérez JA. Dysbiosis and structural disruption of the respiratory microbiota in COVID-19 patients with severe and fatal outcomes. *Sci Rep* 2021; **11**: 21297 [PMID: 34716394 DOI: 10.1038/s41598-021-00851-0]

86 **Han Y**, Jia Z, Shi J, Wang W, He K. The active lung microbiota landscape of COVID-19 patients through the metatranscriptome data analysis. *Bioimpacts* 2022; **12**: 139-146 [PMID: 35411293 DOI: 10.34172/bi.2021.23378]

87 **Rosas-Salazar C**, Kimura KS, Shilts MH, Strickland BA, Freeman MH, Wessinger BC, Gupta V, Brown HM, Rajagopala SV, Turner JH, Das SR. SARS-CoV-2 infection and viral load are associated with the upper respiratory tract microbiome. *J Allergy Clin Immunol* 2021; **147**: 1226-1233.e2 [PMID: 33577896 DOI: 10.1016/j.jaci.2021.02.001]

88 **Nardelli C**, Gentile I, Setaro M, Di Domenico C, Pinchera B, Buonomo AR, Zappulo E, Scotto R, Scaglione GL, Castaldo G, Capoluongo E. Nasopharyngeal Microbiome Signature in COVID-19 Positive Patients: Can We Definitively Get a Role to *Fusobacterium periodonticum*? *Front Cell Infect Microbiol* 2021; **11**: 625581 [PMID: 33659220 DOI: 10.3389/fcimb.2021.625581]

89 **Mostafa HH**, Fissel JA, Fanelli B, Bergman Y, Gniazdowski V, Dadlani M, Carroll KC, Colwell RR, Simner PJ. Metagenomic Next-Generation Sequencing of Nasopharyngeal Specimens Collected from Confirmed and Suspect COVID-19 Patients. *mBio* 2020; **11** [PMID: 33219095 DOI: 10.1128/mBio.01969-20]

90 **Muus C**, Luecken MD, Eraslan G, Sikkema L, Waghray A, Heimberg G, Kobayashi Y, Vaishnav ED, Subramanian A, Smillie C, Jagadeesh KA, Duong ET, Fiskin E, Torlai Triglia E, Ansari M, Cai P, Lin B, Buchanan J, Chen S, Shu J, Haber AL, Chung H, Montoro DT, Adams T, Aliee H, Allon SJ, Andrusivova Z, Angelidis I, Ashenberg O, Bassler K, Bécavin C, Benhar I, Bergenstråhle J, Bergenstråhle L, Bolt L, Braun E, Bui LT, Callori S, Chaffin M, Chichelnitskiy E, Chiou J, Conlon TM, Cuoco MS, Cuomo ASE, Deprez M, Duclos G, Fine D, Fischer DS, Ghazanfar S, Gillich A, Giotti B, Gould J, Guo M, Gutierrez AJ, Habermann AC, Harvey T, He P, Hou X, Hu L, Hu Y, Jaiswal A, Ji L, Jiang P, Kapellos TS, Kuo CS, Larsson L, Leney-Greene MA, Lim K, Litviňuková M, Ludwig LS, Lukassen S, Luo W, Maatz H, Madissoon E, Mamanova L, Manakongtreecheep K, Leroy S, Mayr CH, Mbano IM, McAdams AM, Nabhan AN, Nyquist SK, Penland L, Poirion OB, Poli S, Qi C, Queen R, Reichart D, Rosas I, Schupp JC, Shea CV, Shi X, Sinha R, Sit RV, Slowikowski K, Slyper M, Smith NP, Sountoulidis A, Strunz M, Sullivan TB, Sun D, Talavera-López C, Tan P, Tantivit J, Travaglini KJ, Tucker NR, Vernon KA, Wadsworth MH, Waldman J, Wang X, Xu K, Yan W, Zhao W, Ziegler CGK; NHLBI LungMap Consortium; Human Cell Atlas Lung Biological Network. Single-cell meta-analysis of SARS-CoV-2 entry genes across tissues and demographics. *Nat Med* 2021; **27**: 546-559 [PMID: 33654293 DOI: 10.1038/s41591-020-01227-z]

91 **Patanavanich R**, Glantz SA. Smoking Is Associated With COVID-19 Progression: A Meta-analysis. *Nicotine Tob Res* 2020; **22**: 1653-1656 [PMID: 32399563 DOI: 10.1093/ntr/ntaa082]

92 **Vulturar DM**, Crivii CB, Orăsan OH, Palade E, Buzoianu AD, Zehan IG, Todea DA. Obesity Impact on SARS-CoV-2 Infection: Pros and Cons "Obesity Paradox"-A Systematic Review. *J Clin Med* 2022; **11** [PMID: 35807129 DOI: 10.3390/jcm11133844]

93 **Földi M**, Farkas N, Kiss S, Zádori N, Váncsa S, Szakó L, Dembrovszky F, Solymár M, Bartalis E, Szakács Z, Hartmann P, Pár G, Erőss B, Molnár Z, Hegyi P, Szentesi A; KETLAK Study Group. Obesity is a risk factor for developing critical condition in COVID-19 patients: A systematic review and meta-analysis. *Obes Rev* 2020; **21**: e13095 [PMID: 32686331 DOI: 10.1111/obr.13095]

94 **Jahrami H**, BaHammam AS, Bragazzi NL, Saif Z, Faris M, Vitiello MV. Sleep problems during the COVID-19 pandemic by population: a systematic review and meta-analysis. *J Clin Sleep Med* 2021; **17**: 299-313 [PMID: 33108269 DOI: 10.5664/jcsm.8930]

95 **Li X**, Zhong X, Wang Y, Zeng X, Luo T, Liu Q. Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis. *PLoS One* 2021; **16**: e0250602 [PMID: 33939733 DOI: 10.1371/journal.pone.0250602]

96 **Zayed NE**, Abbas A, Lutfy SM. Criteria and potential predictors of severity in patients with COVID-19. *Egypt J Bronchol* 2022; **16**: 11 [DOI: 10.1186/s43168-022-00116-y]

97 **Debuc B**, Smadja DM. Is COVID-19 a New Hematologic Disease? *Stem Cell Rev Rep* 2021; **17**: 4-8 [PMID: 32399806 DOI: 10.1007/s12015-020-09987-4]

98 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

99 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

100 **Cossarizza A**, De Biasi S, Guaraldi G, Girardis M, Mussini C; Modena Covid-19 Working Group (MoCo19)#. SARS-CoV-2, the Virus that Causes COVID-19: Cytometry and the New Challenge for Global Health. *Cytometry A* 2020; **97**: 340-343 [PMID: 32187834 DOI: 10.1002/cyto.a.24002]

101 **Azar MM**, Shin JJ, Kang I, Landry M. Diagnosis of SARS-CoV-2 infection in the setting of the cytokine release syndrome. *Expert Rev Mol Diagn* 2020; **20**: 1087-1097 [PMID: 32990479 DOI: 10.1080/14737159.2020.1830760]

102 **Ponti G**, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci* 2020; **57**: 389-399 [PMID: 32503382 DOI: 10.1080/10408363.2020.1770685]

103 **Chan JF**, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514-523 [PMID: 31986261 DOI: 10.1016/S0140-6736(20)30154-9]

104 **Chiappetta S**, Sharma AM, Bottino V, Stier C. COVID-19 and the role of chronic inflammation in patients with obesity. *Int J Obes (Lond)* 2020; **44**: 1790-1792 [PMID: 32409680 DOI: 10.1038/s41366-020-0597-4]

105 **Alamdari NM**, Afaghi S, Rahimi FS, Tarki FE, Tavana S, Zali A, Fathi M, Besharat S, Bagheri L, Pourmotahari F, Irvani SSN, Dabbagh A, Mousavi SA. Mortality Risk Factors among Hospitalized COVID-19 Patients in a Major Referral Center in Iran. *Tohoku J Exp Med* 2020; **252**: 73-84 [PMID: 32908083 DOI: 10.1620/tjem.252.73]

106 **Kernan KF**, Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol* 2017; **29**: 401-409 [PMID: 28541437 DOI: 10.1093/intimm/dxx031]

107 **Ruscitti P**, Cipriani P, Di Benedetto P, Liakouli V, Berardicurti O, Carubbi F, Ciccia F, Guggino G, Triolo G, Giacomelli R. H-ferritin and proinflammatory cytokines are increased in the bone marrow of patients affected by macrophage activation syndrome. *Clin Exp Immunol* 2018; **191**: 220-228 [PMID: 28960260 DOI: 10.1111/cei.13057]

108 **Ruddell RG**, Hoang-Le D, Barwood JM, Rutherford PS, Piva TJ, Watters DJ, Santambrogio P, Arosio P, Ramm GA. Ferritin functions as a proinflammatory cytokine via iron-independent protein kinase C zeta/nuclear factor kappaB-regulated signaling in rat hepatic stellate cells. *Hepatology* 2009; **49**: 887-900 [PMID: 19241483 DOI: 10.1002/hep.22716]

109 **Liu W**, Zhang S, Nekhai S, Liu S. Depriving Iron Supply to the Virus Represents a Promising Adjuvant Therapeutic Against Viral Survival. *Curr Clin Microbiol Rep* 2020; **7**: 13-19 [PMID: 32318324 DOI: 10.1007/s40588-020-00140-w]

110 **Linkins LA**, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. *Int J Lab Hematol* 2017; **39** Suppl 1: 98-103 [PMID: 28447414 DOI: 10.1111/ijlh.12665]

111 **Lippi G**, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Intern Med* 2014; **25**: 45-48 [PMID: 23948628 DOI: 10.1016/j.ejim.2013.07.012]

112 **Yao Y**, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care* 2020; **8**: 49 [PMID: 32665858 DOI: 10.1186/s40560-020-00466-z]

113 **Moon AM**, Barritt AS 4th. Elevated Liver Enzymes in Patients with COVID-19: Look, but Not Too Hard. *Dig Dis Sci* 2021; **66**: 1767-1769 [PMID: 32875529 DOI: 10.1007/s10620-020-06585-9]

114 **Nishtar T**, Ullah N, Ahmad FS, Rahim S. Radiographic patterns on Chest X-ray as a supporting imaging tool in triaging of suspected Corona Virus Disease (COVID) patients. *Pak J Med Sci* 2022; **38**: 1639-1643 [PMID: 35991277 DOI: 10.12669/pjms.38.6.5279]

115 **Solomon JJ**, Heyman B, Ko JP, Condos R, Lynch DA. CT of Post-Acute Lung Complications of COVID-19. *Radiology* 2021; **301**: E383-E395 [PMID: 34374591 DOI: 10.1148/radiol.2021211396]

116 **Kameda T**, Mizuma Y, Taniguchi H, Fujita M, Taniguchi N. Point-of-care lung ultrasound for the assessment of pneumonia: a narrative review in the COVID-19 era. *J Med Ultrason (2001)* 2021; **48**: 31-43 [PMID: 33438132 DOI: 10.1007/s10396-020-01074-y]

117 **Smith DL**, Grenier JP, Batte C, Spieler B. A Characteristic Chest Radiographic Pattern in the Setting of the COVID-19 Pandemic. *Radiol Cardiothorac Imaging* 2020; **2**: e200280 [PMID: 33778626 DOI: 10.1148/ryct.2020200280]

118 **Choi H**, Qi X, Yoon SH, Park SJ, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, Park CM, Kim YH, Lei J, Hong JH, Kim H, Hwang EJ, Yoo SJ, Nam JG, Lee CH, Goo JM. Extension of Coronavirus Disease 2019 on Chest CT and Implications for Chest Radiographic Interpretation. *Radiol Cardiothorac Imaging* 2020; **2**: e200107 [PMID: 33778565 DOI: 10.1148/ryct.2020200107]

119 **Khan SA**, Manohar M, Khan M, Asad S, Adil SO. Radiological profile of patients undergoing Chest X-ray and computed tomography scans during COVID-19 outbreak. *Pak J Med Sci* 2021; **37**: 1288-1294 [PMID: 34475900 DOI: 10.12669/pjms.37.5.4290]

120 **Farias LPG**, Fonseca EKUN, Strabelli DG, Loureiro BMC, Neves YCS, Rodrigues TP, Chate RC, Nomura CH, Sawamura MVY, Cerri GG. Imaging findings in COVID-19 pneumonia. *Clinics (Sao Paulo)* 2020; **75**: e2027 [PMID: 32578826 DOI: 10.6061/clinics/2020/e2027]

121 **Wu J**, Wu X, Zeng W, Guo D, Fang Z, Chen L, Huang H, Li C. Chest CT Findings in Patients With Coronavirus Disease 2019 and Its Relationship With Clinical Features. *Invest Radiol* 2020; **55**: 257-261 [PMID: 32091414 DOI: 10.1097/RLI.0000000000000670]

122 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]

123 **Bernheim A**, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020; **295**: 200463 [PMID: 32077789 DOI: 10.1148/radiol.2020200463]

124 **Salahshour F**, Mehrabinejad MM, Nassiri Toosi M, Gity M, Ghanaati H, Shakiba M, Nosrat Sheybani S, Komaki H, Kolahi S. Clinical and chest CT features as a predictive tool for COVID-19 clinical progress: introducing a novel semi-quantitative scoring system. *Eur Radiol* 2021; **31**: 5178-5188 [PMID: 33449185 DOI: 10.1007/s00330-020-07623-w]

125 **Tung-Chen Y**, Martí de Gracia M, Díez-Tascón A, Alonso-González R, Agudo-Fernández S, Parra-Gordo ML, Ossaba-Vélez S, Rodríguez-Fuertes P, Llamas-Fuentes R. Correlation between Chest Computed Tomography and Lung Ultrasonography in Patients with Coronavirus Disease 2019 (COVID-19). *Ultrasound Med Biol* 2020; **46**: 2918-2926 [PMID: 32771222 DOI: 10.1016/j.ultrasmedbio.2020.07.003]

126 **Zieleskiewicz L**, Markarian T, Lopez A, Taguet C, Mohammedi N, Boucekine M, Baumstarck K, Besch G, Mathon G, Duclos G, Bouvet L, Michelet P, Allaouchiche B, Chaumoître K, Di Bisceglie M, Leone M; AZUREA Network. Comparative study of lung ultrasound and chest computed tomography scan in the assessment of severity of confirmed COVID-19 pneumonia. *Intensive Care Med* 2020; **46**: 1707-1713 [PMID: 32728966 DOI: 10.1007/s00134-020-06186-0]

127 **Raptis CA**, Hammer MM, Short RG, Shah A, Bhalla S, Bierhals AJ, Filev PD, Hope MD, Jeudy J, Kligerman SJ, Henry TS. Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date. *AJR Am J Roentgenol* 2020; **215**: 839-842 [PMID: 32298149 DOI: 10.2214/AJR.20.23202]

128 **Campagnano S**, Angelini F, Fonsi GB, Novelli S, Drudi FM. Diagnostic imaging in COVID-19 pneumonia: a literature review. *J Ultrasound* 2021; **24**: 383-395 [PMID: 33590456 DOI: 10.1007/s40477-021-00559-x]

129 **Nouvenne A**, Zani MD, Milanese G, Parise A, Baciarello M, Bignami EG, Odone A, Sverzellati N, Meschi T, Ticinesi A. Lung Ultrasound in COVID-19 Pneumonia: Correlations with Chest CT on Hospital admission. *Respiration* 2020; **99**: 617-624 [PMID: 32570265 DOI: 10.1159/000509223]

130 **Moro F**, Buonsenso D, Moruzzi MC, Inchingolo R, Smargiassi A, Demi L, Larici AR, Scambia G, Lanzone A, Testa AC. How to perform lung ultrasound in pregnant women with suspected COVID-19. *Ultrasound Obstet Gynecol* 2020; **55**: 593-598 [PMID: 32207208 DOI: 10.1002/uog.22028]

131 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? *J Ultrasound Med* 2020; **39**: 1459-1462 [PMID: 32198775 DOI: 10.1002/jum.15284]

132 **Gibbons RC**, Magee M, Goett H, Murrett J, Genninger J, Mendez K, Tripod M, Tyner N, Costantino TG. Lung Ultrasound vs. Chest X-Ray Study for the Radiographic Diagnosis of COVID-19 Pneumonia in a High-Prevalence Population. *J Emerg Med* 2021; **60**: 615-625 [PMID: 33722414 DOI: 10.1016/j.jemermed.2021.01.041]

133 **Peng QY**, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; **46**: 849-850 [PMID: 32166346 DOI: 10.1007/s00134-020-05996-6]

134 **Allinovi M**, Parise A, Giacalone M, Amerio A, Delsante M, Odone A, Franci A, Gigliotti F, Amadasi S, Delmonte D, Parri N, Mangia A. Lung Ultrasound May Support Diagnosis and Monitoring of COVID-19 Pneumonia. *Ultrasound Med Biol* 2020; **46**: 2908-2917 [PMID: 32807570 DOI: 10.1016/j.ultrasmedbio.2020.07.018]

135 **Mohamed MFH**, Al-Shokri S, Yousaf Z, Danjuma M, Parambil J, Mohamed S, Mubasher M, Dauleh MM, Hasanain B, AlKahlout MA, Abubeker IY. Frequency of Abnormalities Detected by Point-of-Care Lung Ultrasound in Symptomatic COVID-19 Patients: Systematic Review and Meta-Analysis. *Am J Trop Med Hyg* 2020; **103**: 815-821 [PMID: 32500849 DOI: 10.4269/ajtmh.20-0371]

136 **Quarato CMI**, Mirijello A, Lacedonia D, Russo R, Maggi MM, Rea G, Simeone A, Borelli C, Feragalli B, Scioscia G, Barbaro MPF, Massa V, De Cosmo S, Sperandeo M. Low Sensitivity of Admission Lung US Compared to Chest CT for Diagnosis of Lung Involvement in a Cohort of 82 Patients with COVID-19 Pneumonia. *Medicina (Kaunas)* 2021; **57** [PMID: 33806432 DOI: 10.3390/medicina57030236]

137 **Bar S**, Lecourtois A, Diouf M, Goldberg E, Bourbon C, Arnaud E, Domisse L, Dupont H, Gosset P. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. *Anaesthesia* 2020; **75**: 1620-1625 [PMID: 32520406 DOI: 10.1111/anae.15175]

138 **Prasad R**, Patton MJ, Floyd JL, Fortmann S, DuPont M, Harbour A, Wright J, Lamendella R, Stevens BR, Oudit GY, Grant MB. Plasma Microbiome in COVID-19 Subjects: An Indicator of Gut Barrier Defects and Dysbiosis. *Int J Mol Sci* 2022; **23** [PMID: 36012406 DOI: 10.3390/ijms23169141]

139 **Allali I**, Bakri Y, Amzazi S, Ghazal H. Gut-Lung Axis in COVID-19. *Interdiscip Perspect Infect Dis* 2021; **2021**: 6655380 [PMID: 33777139 DOI: 10.1155/2021/6655380]

140 **Han H**, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F, Jiang Y, Cheng X, Zhu C, Xia Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect* 2020; **9**: 1123-1130 [PMID: 32475230 DOI: 10.1080/22221751.2020.1770129]

141 **Salazar N**, Arboleya S, Fernández-Navarro T, de Los Reyes-Gavilán CG, Gonzalez S, Gueimonde M. Age-Associated Changes in Gut Microbiota and Dietary Components Related with the Immune System in Adulthood and Old Age: A Cross-Sectional Study. *Nutrients* 2019; **11** [PMID: 31370376 DOI: 10.3390/nu11081765]

142 **Sanchez-Morate E**, Gimeno-Mallench L, Stromsnes K, Sanz-Ros J, Román-Domínguez A, Parejo-Pedrajas S, Inglés M, Olaso G, Gambini J, Mas-Bargues C. Relationship between Diet, Microbiota, and Healthy Aging. *Biomedicines* 2020; **8** [PMID: 32823858 DOI: 10.3390/biomedicines8080287]

143 **Musso G**, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care* 2010; **33**: 2277-2284 [PMID: 20876708 DOI: 10.2337/dc10-0556]

144 **Teuwen LA**, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020; **20**: 389-391 [PMID: 32439870 DOI: 10.1038/s41577-020-0343-0]

145 **Wang H**, Wang H, Sun Y, Ren Z, Zhu W, Li A, Cui G. Potential Associations Between Microbiome and COVID-19. *Front Med (Lausanne)* 2021; **8**: 785496 [PMID: 35004750 DOI: 10.3389/fmed.2021.785496]

146 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]

147 **Effenberger M**, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, Hilbe R, Seiwald S, Scholl-Buergi S, Fritsche G, Bellmann-Weiler R, Weiss G, Müller T, Adolph TE, Tilg H. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; **69**: 1543-1544 [PMID: 32312790 DOI: 10.1136/gutjnl-2020-321388]

148 **Zuo T**, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology* 2020; **159**: 944-955.e8 [PMID: 32442562 DOI: 10.1053/j.gastro.2020.05.048]

149 **Dang AT**, Marsland BJ. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol* 2019; **12**: 843-850 [PMID: 30976087 DOI: 10.1038/s41385-019-0160-6]

150 **Flint HJ**, Scott KP, Duncan SH, Louis P, Forano E. Microbial degradation of complex carbohydrates in the gut. *Gut Microbes* 2012; **3**: 289-306 [PMID: 22572875 DOI: 10.4161/gmic.19897]

151 **Conte L**, Toraldo DM. Targeting the gut-lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. *Ther Adv Respir Dis* 2020; **14**: 1753466620937170 [PMID: 32600125 DOI: 10.1177/1753466620937170]

152 **Xu L**, Yang CS, Liu Y, Zhang X. Effective Regulation of Gut Microbiota With Probiotics and Prebiotics May Prevent or Alleviate COVID-19 Through the Gut-Lung Axis. *Front Pharmacol* 2022; **13**: 895193 [PMID: 35548347 DOI: 10.3389/fphar.2022.895193]

153 **Zhang L**, Han H, Li X, Chen C, Xie X, Su G, Ye S, Wang C, He Q, Wang F, Huang F, Wang Z, Wu J, Lai T. Probiotics use is associated with improved clinical outcomes among hospitalized patients with COVID-19. *Therap Adv Gastroenterol* 2021; **14**: 17562848211035670 [PMID: 34394726 DOI: 10.1177/17562848211035670]

154 **Tang H**, Bohannon L, Lew M, Jensen D, Jung SH, Zhao A, Sung AD, Wischmeyer PE. Randomised, double-blind, placebo-controlled trial of Probiotics To Eliminate COVID-19 Transmission in Exposed Household Contacts (PROTECT-EHC): a clinical trial protocol. *BMJ Open* 2021; **11**: e047069 [PMID: 33952552 DOI: 10.1136/bmjopen-2020-047069]

155 **Ivashkin V**, Fomin V, Moiseev S, Brovko M, Maslennikov R, Ulyanin A, Sholomova V, Vasilyeva M, Trush E, Shifrin O, Poluektova E. Efficacy of a Probiotic Consisting of Lacticaseibacillus rhamnosus PDV 1705, Bifidobacterium bifidum PDV 0903, Bifidobacterium longum subsp. infantis PDV 1911, and Bifidobacterium longum subsp. longum PDV 2301 in the Treatment of Hospitalized Patients with COVID-19: a Randomized Controlled Trial. *Probiotics Antimicrob Proteins* 2021 [PMID: 34643888 DOI: 10.1007/s12602-021-09858-5]

156 **Annweiler C**, Hanotte B, Grandin de l'Eprevier C, Sabatier JM, Lafaie L, Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. *J Steroid Biochem Mol Biol* 2020; **204**: 105771 [PMID: 33065275 DOI: 10.1016/j.jsbmb.2020.105771]

157 **Entrenas Castillo M**, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, Quesada Gomez JM. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol* 2020; **203**: 105751 [PMID: 32871238 DOI: 10.1016/j.jsbmb.2020.105751]

158 **Di Pierro F**, Iqtadar S, Khan A, Ullah Mumtaz S, Masud Chaudhry M, Bertuccioli A, Derosa G, Maffioli P, Togni S, Riva A, Allegrini P, Khan S. Potential Clinical Benefits of Quercetin in the Early Stage of COVID-19: Results of a Second, Pilot, Randomized, Controlled and Open-Label Clinical Trial. *Int J Gen Med* 2021; **14**: 2807-2816 [PMID: 34194240 DOI: 10.2147/IJGM.S318949]

**Footnotes**

**Conflict-of-interest statement:** All authors report having no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 19, 2022

**First decision:** October 19, 2022

**Article in press:** November 16, 2022

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Romania

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Kalani M, Iran; Lee S, South Korea; Papazafiropoulou A, Greece **S-Editor:** Wang JJ **L-Editor:** Filipodia **P-Editor:** Wang JJ

**Table 1 Variants of concern reported for coronavirus disease 2019**

|  |  |  |
| --- | --- | --- |
| **VOCs** | **First time reported** | **Country of origin** |
| Alpha (B.1.1.7) | December 2020 | United Kingdom |
| Beta (B.1.351) | December 2020 | South Africa |
| Gamma (P.1) | January 2021 | Brazil |
| Delta (B.1.617.2) | December 2020 | India |
| Omicron (B.1.1.529) | November 2021 | South Africa |

VOC: Variants of concern.

**Table 2 Changes in gut and airway microbiota bacterial species during coronavirus disease 2019**

|  |  |  |  |
| --- | --- | --- | --- |
| **Changes** | **COVID-19 *vs* non-COVID-19 patients** | **Number of patients COVID-19 *vs* non-COVID-19** | **Ref.** |
| **Gut microbiota** | Increase: *Ruminococcus gnavus*, *Ruminococcus torque*, *Bacteroides dorei* | 100 *vs* 78 | [20] |
| Decrease: *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii*, *Eubacterium rectale* |
| Increase: *Streptococcus*, *Rothia*, *Veillonella*, *Actinomyces* | 30 *vs* 30 | [80] |
| Increase: *Blautia*, *Coprococcus*, *Collinsella* | 53 *vs* 76 | [81] |
| Decrease: *Streptococcus*, *Weissella*, *Enterococcus*, *Rothia*, *Lactobacillus*, *Actinomyces* |
| Increase: *Bifidobacterium*, *Bacteroides*, *Parabacteroides*, *Escherichia-Shigella* | 22 *vs* 40 | [82] |
| Decrease: *Faecalibacterium*, *Dorea*, *Enterobacter* |
| Increase: *Corynebacterium*, *Campylobacter*, *Klebsiella* | 50 *vs* 34 | [83] |
| Increase: *Streptococcus*, *Clostridium*, *Lactobacillus*, *Bifidobacterium* | 64 *vs* 40 | [84] |
| Decrease: *Bacteroidetes*, *Roseburia*, *Faecalibacterium*, *Coprococcus*, *Parabacteroides* |
| **Airway microbiota** | Increase: *Veillonella*, *Staphylococcus*, *Corynebacterium*, *Neisseria*, *Actinobacillus*, *Selenomonas* | 192 *vs* 95 | [85] |
| Decrease: *Haemophilus*, *Alloiococcus* |
| Increase: *Lactobacillus fermentum*, *Lactobacillus reuteri*, *Lactobacillus delbrueckii*, *Lactobacillus salivarius* | 19 *vs* 23 | [86] |
| Increase: *Corynebacterium\_1*, *Staphylococcus*, *Dolosigranulum*, *Peptoniphilus*, *Lawsonella* | 38 *vs* 21 | [87] |
| Decrease: *Leptotrichia*, *Fusobacterium* (especially *Fusobacterium periodonticum*), *Haemophilus* | 18 *vs* 12 | [88] |
| Increase: *Propionibacteriaceae* | 31 *vs* 9 | [89] |
| Decrease: *Corynebacterium accolens* |

COVID-19: Coronavirus disease 2019.

**Table 3 Biomarkers associated with coronavirus disease 2019**

|  |  |
| --- | --- |
| **Decreased levels** | **Increased levels** |
| Lymphocytes | White blood cells |
| Platelets | D-dimers |
| Eosinophils | Fibrinogen |
| C-reactive protein |
| Procalcitonin |
| Lactate dehydrogenase |
| Ferritin |
| IL-6 |
| ALT, AST |
| Alkaline phosphatase |
| Total bilirubin |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IL-6: Interleukin 6.

**Table 4 Nutraceuticals used to improve disease severity and outcomes of coronavirus disease 2019 patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Nutraceuticals** | **Number of patients with *vs* without nutraceutical agent** | **Results** | **Ref.** |
| Probiotic combined *Bifidobacterium*, *Lactobacillus* and *Enterococcus* | 179 *vs* 196 | Shorter time to clinical improvement (fever, hospital stay, viral shedding) in hospitalized COVID-19 subjects | [153] |
| Probiotic *Lactobacillus hamnosus* GG | 566 *vs* 566 | Extended time until the development of infection with COVID-19, reduced the severity of the disease, changed the composition of the intestinal microbiota in the household contact infected with COVID-19 (after 28 d) | [154] |
| Probiotic *Lacticaseibacillus rhamnosus*, *Bifidobacterium bifidum*, *Bifidobacterium longum subsp. infantis*, *Bifidobacterium longum subsp. longum* | 99 *vs* 101 | The duration of diarrhea was shorter in patients who received the probiotic than in those who did not. No significant effect on mortality, no change in most biomarkers in patients with COVID-19 in hospitalized patients (at 14 d) | [155] |
| Vitamin D3 (single oral bolus of 80000 IU) | 57 *vs* 9 | The severity of COVID-19 decreased. Improved survival rate | [156] |
| 25-hydroxyvitamin D3 | 50 *vs* 26 | Reduced the need for treatment in the ICU in patients hospitalized due to proven COVID-19 | [157] |
| Quercetin | 21 *vs* 21 | Decreased virus clearance, frequency of symptoms and level of LDH and ferritin parameters | [158] |

ICU: Intensive care unit; LDH: Lactate dehydrogenase; COVID-19: Coronavirus disease 2019.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**