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ORIGINAL

Correlations Between Gut Microbiome Changes, Gut Barrier Function, and Immune Homeostasis in COVID-19 Patients: The Role of Gut Microbiota in Immunity and Cancer Prevention

Correlaciones entre los cambios del microbioma intestinal, la función de barrera intestinal y la homeostasis inmunitaria en pacientes con COVID-19: El papel del microbiota intestinal en la inmunidad y la prevención del cáncer

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ABSTRACT

Systemic inflammation and immunological dysregulation are linked to COVID-19 infection, and there is mounting evidence that gut barrier failure and gut microbiota dysbiosis are related. Gaining knowledge of these relationships could help explain how diseases develop. By measuring biomarkers and cytokine levels, this research aims to analyze the relationships among gut microbiota alterations, gut barrier function, and immunological homeostasis in COVID-19 patients. Using IBM SPSS (version 26) with Pearson Correlation, Chi-Square testing, independent t-tests, and Multivariate Regression analysis, a comparative study was conducted using gut barrier biomarkers (Zonulin, LPS, I-FABP) and cytokine levels (IL-6, IL-10, TNF-α). In COVID-19 individuals, there were notable variations in gut barrier biomarkers and cytokine levels, with robust associations suggesting a connection between immune dysregulation and gut barrier failure. Gut microbiota dysbiosis and gut barrier dysfunction are significantly associated with immune homeostasis disturbance in COVID-19 patients, which may be a contributing factor to the disease's severity and progression.

Keywords: Acute Invasive Fungal Rhino-Sinusitis; Inpatients; Epidemiology; Pathogen Diversity; Coexisting Infections.

RESUMEN

La inflamación sistémica y la desregulación inmunológica están vinculadas a la infección por COVID-19, y cada vez hay más pruebas de que el fallo de la barrera intestinal y la disbiosis del microbiota intestinal están relacionados. Conocer estas relaciones podría ayudar a explicar cómo se desarrollan las enfermedades. Mediante la medición de biomarcadores y niveles de citocinas, esta investigación pretende analizar las relaciones entre las alteraciones del microbiota intestinal, la función de barrera intestinal y la homeostasis inmunológica en pacientes con COVID-19. Utilizando IBM SPSS (versión 26) con correlación de Pearson, pruebas de Chi-cuadrado, pruebas t independientes y análisis de regresión multivariante, se realizó un estudio comparativo utilizando biomarcadores de barrera intestinal (Zonulina, LPS, I-FABP) y niveles de citocinas (IL-6, IL-10,

TNF-α). En los individuos COVID-19 se observaron notables variaciones en los biomarcadores de la barrera intestinal y los niveles de citocinas, con asociaciones sólidas que sugieren una conexión entre la desregulación inmunitaria y el fallo de la barrera intestinal. La disbiosis del microbiota intestinal y la disfunción de la barrera intestinal están significativamente asociadas con la alteración de la homeostasis inmunitaria en pacientes con COVID-19, lo que puede ser un factor que contribuya a la gravedad y progresión de la enfermedad.

Palabras clave: Rinosinusitis Fúngica Invasiva Aguda; Pacientes Hospitalizados; Epidemiología; Diversidad de Patógenos; Infecciones Coexistentes.

INTRODUCTION

Acute Respiratory Severity The novel and highly contagious coronavirus 2 (SARS-CoV-2) that causes severe acute respiratory syndrome is the cause of Coronavirus Disease 2019 (COVID-19).[1] The severity of the condition is strongly correlated with elderly age, diabetes, immunological indications, and the impact of comorbidities, according to recent epidemiological data.[2] Dyspnea, infection, cough, and sore throat are the most prevalent clinical presentations of COVID-19, which most often affects the pulmonary system. Clinical indicators can range greatly, from multi-organ failure and death to the lack of symptoms.[3] Pneumonia, the condition known as acute hypoxic respiratory failure, and even death could complicate a patient's clinical trajectory in more severe circumstances.[4] It should be noted that the strong cytokine and chemokine response produced by SARS-CoV2 significantly influences the development of acute respiratory distress syndrome (ARDS).[5] COVID-19 individuals also experience extrapulmonary difficulties from the Gastrointestinal (GI), hepatobiliary, renal, with neurologic systems, albeit respiratory symptoms are the most commonly reported. Additionally, a small percentage of people could develop autoinflammatory symptoms upon recovery, including pediatric Kawasaki-like disease and multisystem inflammatory syndrome.[6]

Research has demonstrated that the protein of SARS-CoV-2 is an essential site of entry into the host. As a result of this relationship, infecting de novo viral particles are produced and replicated more frequently.[7,8,9] The heart, kidneys, lungs, and intestinal epithelial cells express these receptors at high levels. This suggests that by preserving amino-acid transporters, ACE2 regulates intestinal resistance and the structure of the gut microbiota.[10] The importance of the gut-lung axis, which involves the microbiome, must thus be considered in the context of SARS-CoV-2 infection. According to recent studies, there could be communication involving the gut and the lungs because COVID-19 infection can be found in anal/rectal swabs and fecal specimens in addition to mouth swabs.[11] There is mounting evidence that the gut and lung bacteria interact well, which is essential for preserving homeostasis.[12] Changes in the microbial ecology thereby induce persistent low-grade inflammation and enhance host vulnerability and disease outcomes. However, previous research investigations have similarly established the effect of dysbiosis on the allergic reactions associated with the disease.[13]

The work examined that rigorous analysis was due to Corona virus breakdown of the gastrointestinal barrier, corona individuals develop viral sepsis. Increased intestinal permeability, immune cell activation, and the introduction of endo-toxins, fungus, and luminal bacteria into the bloodstream were the results.[14] That problem could be completely worse in people with comorbidities by endotoxemia and pre-existing gut barrier failure. According to the analysis, COVID-19 interferes with the gut-lung bloc which impacts the significance of the GI system and the gut barrier.[15] Those cells were damaged by SARS-CoV-2 which interferes with immune responses and impairs the respiratory immune system's capacity to prevent viral infection. Due to immune thrombosis, severe thrombotic consequences, and increased intestinal permeability, the intestinal vasculature becomes hyper-inflamed and the immune system overreacts. Research examined how different illnesses including the COVID-19 pandemic, could impact the composition and functionality of the intestinal barrier. The imbalance of the microbiota in the intestines or disturbance of barrier function could impact the course and severity of the medical condition.[16] An overview of the gut changes associated with human illnesses, such as COVID-19, was also presented, along with supporting therapy approaches that could assist in restoring intestinal barrier function and perhaps enhance patient outcomes. Research examined the gastrointestinal and respiratory tracts containing human microorganisms that impact immune system responses and metabolism.[17] Breathing issues could be caused by lung health issues and inflammation mediated by SARS-CoV-2 that was dependent on the gastric pulmonary nexus. Research evaluated that lung disorders were related to the microbiota in the stomach and infections caused by respiratory viruses could distress. Several variables, including nutrition, environment, and genetics, could affect susceptibility as well as affect the gut flora. The majority of elderly individuals were at risk from 2019-nCoV, although its effects could be mitigated by enhancing the gut flora with individualized supplements and diet.[18]

Co-supplementing functional foods with existing medicines could be the subject of future investigations. The micro-biota facilitates the investigation's analysis of mucosal homeostasis, resistance, the upper respiratory

tract, and nasal barrier were critical components of infection prevention.[19] Lowering the virus's transmission and improving symptoms could be achieved by reestablishing the natural barriers and anti-inflammatory nature processes that COVID-19 individuals had lost. Research analyzed the coronavirus puts older people and a small child at increased risk, but that makes men more sensitive and causes severe symptoms. Inflammatory cell recruitment and released cytokines were frequent symptoms in the gastrointestinal system.[20] The principal cause of intestinal injury was the binding of the SARS-associated to the receptors for ACE2. Inflammatory bowel disease (IBD) patients were not more likely to get COVID-19 infection.[21] Research evaluated the immune-modulating properties of HGM and the studies on probiotics of the next generation for treating and preventing COVID-19. Globally, the pandemic was predicted to have a major influence on depression and TB rates. Vaccine effectiveness could be predicted by HGM dysfunction. Rehabilitation strategies should be considered as the use of specialized functional foods and next-generation pharmabiotic's.[22]

Research fecal models from 13 COVID-19 patients with controls were subjected to shotgun metagenomic or meta-transcriptomic sequencing. It examined the gut microbiota's structure, found the distinctive microorganisms, and chose biomarkers. This retrospective, qualitative investigation additionally assessed the impact of continuous spore-based probiotic therapy on the experimental results of restrained COVID-19 [23] as well. Data on COVID-19 symptoms, probiotic use, medical history, and demographics were gathered. Time-to-symptom resolution was the main endpoint, with the presence of digestive symptoms and time-to-fever resolution as secondary outcomes. The research's [24] objectives were to compare gut microbiota profiles between improved patients with healthy controls, evaluate microbial diversity, and identify particular bacterial species linked to COVID-19.

Objective of the research

Examining the relationships among gut microbiota alterations, gut barrier function, and immunological homeostasis in COVID-19 patients is the determination of this research. Evaluating the effects of gut microbiota alterations on intestinal permeability and systemic inflammation is the purpose. To comprehend the role of gut barrier failure in immunological dysregulation, research measures cytokine levels and gut barrier biomarkers.

METHOD

Research participants

The clinical data utilized in this investigation included 70 COVID-19 patients from Group A along with 40 non-infected controls from Group B. The analytical assessment between groups becomes possible through the inclusion of clinical and demographic parameters in the data. Research aims to clarify the relationships between immunological stability and gut barrier operation and modifications to the gut microbiome. The evaluation of variations in participants helps expose vital connections between COVID-19 and both immune system activity and gastrointestinal wellness. table 1 shows that the demographic details of patients.

Analysis of the Gut Microbiota in the groups

Research utilizes sequencing platforms like Illumina MiSeq or Ion Torrent to perform 16S rRNA sequencing or metagenomic sequencing on stool samples from Group A and Group B to aspect into changes in the gut microbiome. Biomedical programs Microbiome Analyst and QIIME2 will process the analysis of microbial features and diversity. The evaluation of microbial variants between and within groups will be conducted through alpha and beta diversity examinations. The method will help identify gut microbiota irregularities in COVID-19 patients while showing their connection to disease seriousness and immune system issues.

Evaluating the Gut Barrier's Integrity

Intestinal Fatty Acid Binding Protein (I-FABP), intestinal permeability, lipopolysaccharide (LPS) tests, and zonulin evaluation are all necessary for evaluating the function of the gut barrier. Additional biochemical examinations including ELISA will assess serum and fecal indicators by utilizing this technique. The analysis will demonstrate how well the intestinal barrier performs and disease progression by measuring Gut barrier integrity between Group A and Group B.

Evaluation of Immune Homeostasis

The experimental analysis of cytokines IL-6, IL-10, and TNF-α will rely on ELISA or multiplex assays for detection purposes which assess immune homeostasis. Flow cytometry analysis will serve to check immune cell distributions and reactiveness through immune cell profiling procedures. The investigation of Group A and Group B immune responses helps discover additional information about COVID-19 immune dysregulation patterns as well as gut barrier and microbiome changes.

Table 1. Clinical and Demographic Aspects of Non-Infected Controls and COVID-19 Patients.

Variable	Category	Group A (COVID-19 Patients) (n=70)	Group B (Non-Infected Controls) (n=40)
Age	<30	17	8
	30-50	35	20
	>50	18	12
Gender	Male	42	22
	Female	28	18
COVID-19 Severity	Mild	30	-
	Moderate	25	-
	Severe	15	-
Comorbidities	None	25	28
	Diabetes	15	5
	Hypertension	15	4
	Others	15	3
Smoking Status	Smoker	20	6
	Non-smoker	50	34
Alcohol Consumption	None	40	30
	Occasionally	20	7
	Regularly	10	3
Gastrointestinal Symptoms	Yes	30	5
	No	40	35
ICU Admission	Yes	18	-
	No	52	-
Ventilation support	Yes	12	-
	No	58	-
Antibiotic use	Yes	40	5
	No	30	35

Statistics analysis

A statistical evaluation through IBM SPSS Statistics version 28 will investigate the immune system balance gut barrier status and gut microbial diversity of subjects between Groups A and B. Comparison of continuous variables between the two groups will be measured with an independent t-test for mean differences assessment. Statistical analysis will utilize the Chi-Square Test to study relationships between categorical factors of gastrointestinal symptoms and comorbidities and COVID-19 status. Pearson Correlation Analysis will evaluate the relationships regarding intestinal permeability marker associations, immune response indicator associations, and gut microbiome diversity indicators while determining their direction and intensity. The Multivariate Regression Analysis will identify essential predictors of immunological dysregulation through controlling variables including age body mass index and comorbidities which provide an understanding of gut-immune system relations.

RESULTS AND DISCUSSION

Effects of an independent t-test comparing the levels of cytokines and gut barrier biomarkers in groups A and B

To examine the participation of gut microbiome dysbiosis with gut barrier dysfunction in the pathogenesis of COVID-19, the gut barrier biomarkers and cytokine levels of Group A and Group B were associated using the independent t-test and are presented in table 2 and figure 1. All measured parameters, including Zonulin, LPS, I-FABP, IL-6, IL-10, and TNF-α, showed significant differences. These results imply that Group A differs from Group B in that immunological homeostasis disruption could be a result of gut microbiome dysbiosis and gut barrier dysfunction.

Chi-Square Test Results for Categorical Variables within the Groups

A Chi-Square Test analyzed correlations between categorized variables across Group A and Group B that involved gastrointestinal symptoms and comorbidities antibiotic treatment and ICU hospitalization and breathing aid requirements. Figure 2 and table 3 demonstrates significant associations between comorbidities ($p = 0,007$) antibiotic prescriptions ($p = 0,003$) intensive care unit admissions ($p = 0,038$) and gastrointestinal symptoms ($p = 0,026$). The influence of infection on clinical outcomes is demonstrated by these findings, which

imply that Patients with COVID-19 are more inclined to acquire gastrointestinal indications, need antibiotics, and have higher ICU admission rates.

Table 2. Gut Barrier and Cytokine Level Comparison Between Group A and Group B.

Variable	Group A (COVID-19 Patients)	Group B (Non-Infected Controls)	Mean Difference	t-Value	p-Value
Zonulin (ng/mL)	52,4 ± 8,3	35,7 ± 5,1	16,7	5,92	<0,001**
LPS (pg/mL)	130,5 ± 15,2	85,4 ± 10,7	45,1	7,23	<0,001**
I-FABP (pg/mL)	420,3 ± 35,4	300,6 ± 25,8	119,7	8,15	<0,001**
IL-6 (pg/mL)	72,8 ± 10,5	25,6 ± 6,8	47,2	9,30	<0,001**
IL-10 (pg/mL)	14,2 ± 2,4	10,1 ± 1,7	4,1	4,28	0,002**
TNF-α (pg/mL)	48,6 ± 7,8	22,4 ± 5,6	26,2	6,87	<0,001**

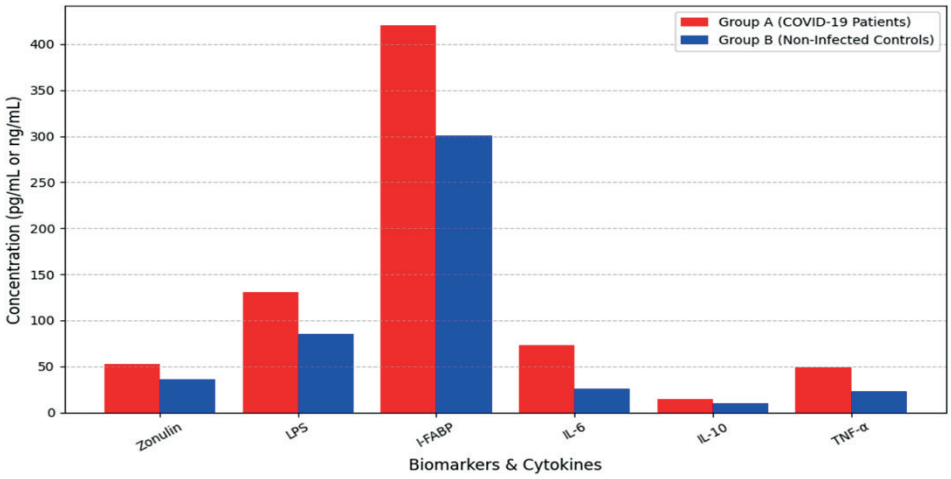

Figure 1. Comparison of Cytokine Levels and Gut Barrier Biomarkers

Table 3. Significant Associations of Categorical Variables between Group A and B.

Variable	Category	Group A (n=70)	Group B (n=40)	Chi-Square (x^2)	p-Value
Gastrointestinal Symptoms	Yes	30	5	7,23	0,026*
	No	40	35		
Comorbidities	Yes	45	12	10,33	0,007**
	No	25	28		
Antibiotic use	Yes	40	5	11,58	0,003**
	No	30	35		
ICU Admission	Yes	18	-	6,54	0,038*
	No	52	40		
Ventilation support	Yes	12	-	3,98	0,055
	No	58	40		

Pearson Correlation Analysis between Gut Barrier Biomarkers, Cytokine Levels, and Gut Microbiome Variation in Group A

To investigate their role in immune homeostasis disruption, this Analysis was used to assess the associations among gut barrier dysfunction, inflammatory cytokine levels, and gut microbiome diversity in Group A (COVID-19 patients). Group A was the only group for which this analysis was done since these pathological alterations are most significant when COVID-19 infection is present. Zonulin and IL-6, LPS and TNF-α, and Zonulin and Gut Microbiome Diversity showed significant correlations (figure 3 and table 4), suggesting a possible connection between inflammation, gut barrier dysfunction, and microbiome changes in COVID-19 patients.

Multivariate Regression Analysis of Gut Barrier Biomarkers Associated with Cytokine Levels in Group A

To determine their significance in immunological dysregulation, multivariate regression analysis was utilized to examine the affliction between gut barrier biomarkers with cytokine levels in Group A (COVID-19 patients).

Since gut barrier failure and inflammatory responses are largely shown in COVID-19 infection, this analysis was only conducted for Group A. Zonulin and IL-6, LPS and TNF-α, and Zonulin and IL-10 were shown (table 5) to have significant relationships, suggesting that disturbance of the gut barrier affects immune response.

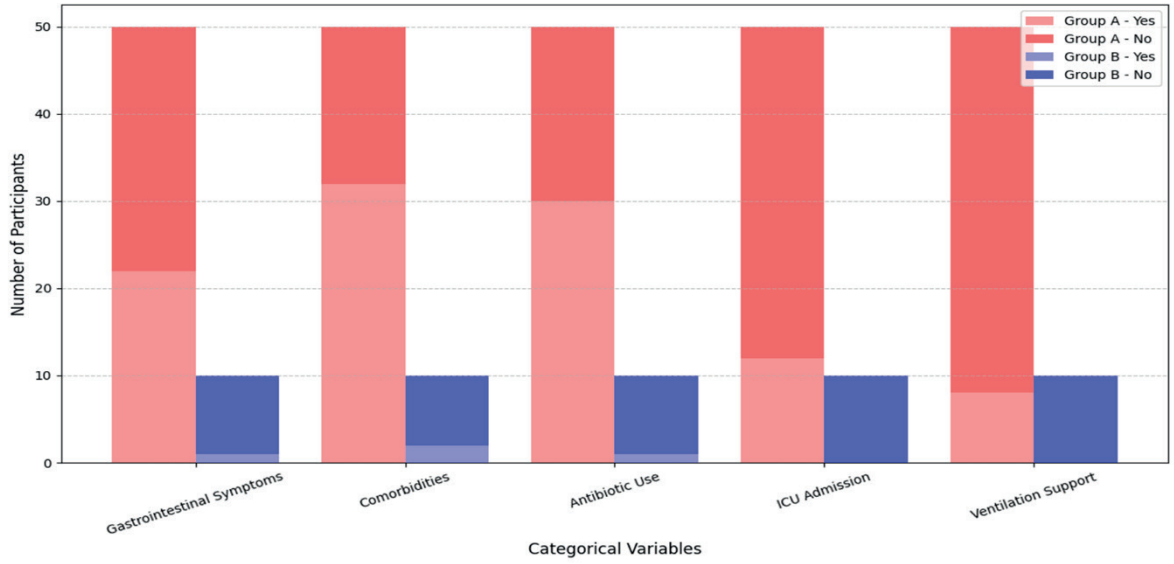

Figure 2. Results of the Chi-Square Test Indicating Group Differences

Table 4. Association of Cytokine Levels, Gut Barrier Biomarkers, and Microbiome Diversity in Group A

Variable 1	Variable 2	Correlation Coefficient (r)	p-Value
Zonulin (ng/mL)	IL-6 (pg/mL)	0,72	<0,001**
LPS (pg/mL)	TNF-α (pg/mL)	0,68	<0,001**
I-FABP (pg/mL)	IL-10 (pg/mL)	0,45	0,004**
Zonulin (ng/mL)	Gut Microbiome Diversity	-0,55	0,002
LPS (pg/mL)	Gut Microbiome Diversity	-0,60	<0,001**
I-FABP (pg/mL)	Gut Microbiome Diversity	-0,48	0,006**

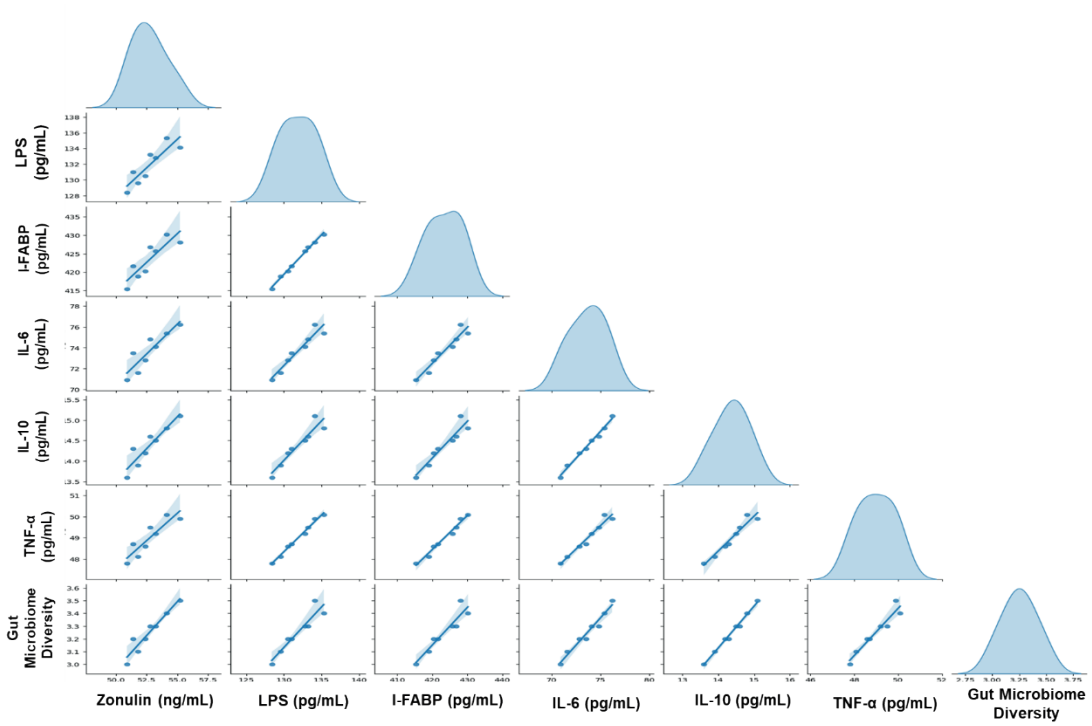

Figure 3. Correlation Analysis of Biomarkers, Cytokines, and Gut Microbiome Diversity in Group A

Table 5. Correlation between Group A's Cytokine Levels and Gut Barrier Biomarkers.

Dependent Variable	Independent Variable	Regression Coefficient (ß)	Standard Error	t-Value	p-Value
IL-6 (pg/mL)	Zonulin (ng/mL)	0,68	0,12	5,67	<0,001**
	LPS (pg/mL)	0,55	0,10	5,50	<0,001**
	I-FABP (pg/mL)	0,32	0,08	4,00	0,001**
TNF-α (pg/mL)	Zonulin (ng/mL)	0,60	0,11	5,45	<0,001**
	LPS (pg/mL)	0,50	0,09	5,56	<0,001**
	I-FABP (pg/mL)	0,29	0,07	4,14	0,002**
IL-10 (pg/mL)	Zonulin (ng/mL)	-0,25	0,09	-2,78	0,011**
	LPS (pg/mL)	-0,22	0,08	-2,75	0,012*
	I-FABP (pg/mL)	-0,15	0,06	-2,50	0,018*

By comparing gut barrier biomarkers and cytokine levels between Group A and Group B, this research aimed to determine that gut microbiome dysbiosis, gut barrier dysfunction, and immunological homeostasis disruption contribute to the mechanism of COVID-19. There were notable differences in cytokine levels and gut barrier biomarkers, suggesting that COVID-19 infection is linked to elevated intestinal permeability and systemic inflammation. In COVID-19 patients, categorical characteristics such as comorbidities, ICU hospitalizations, and gastrointestinal complaints also demonstrated significant correlations. Strong connections between impaired intestinal barrier function and increased inflammatory responses were also shown by correlation analysis. Regression analysis supported the idea that gut barrier dysfunction is a key factor in the mechanism of disease of COVID-19 by highlighting the impact of compromised gut block integrity on immunological dysregulation.

CONCLUSION

By contrasting Group A (COVID-19 patients) with Group B (non-infected controls), this research aimed to assess the character of gut microbiome dysbiosis, gut block dysfunction, with immunological homeostasis disturbance in the mechanism of COVID-19. There were notable variations in the levels of gut barrier biomarkers and cytokines, such as TNF-α, LPS, I-FABP, IL-6, IL-10, and Zonulin. Furthermore, there were notable variations in categorical characteristics such as ICU admission ($p = 0,038$), comorbidities ($p = 0,007$), antibiotic use ($p = 0,003$), and gastrointestinal symptoms ($p = 0,026$). Strong positive connections were found between Zonulin and IL-6, LPS and TNF-α, and gut barrier biomarkers and microbiome diversity (Zonulin: $r = -0,55$, $p = 0,002$), according to correlation analysis. Regression analysis also demonstrated a substantial correlation between Zonulin and IL-6 ($ß = 0,68$, $p < 0,001$), confirming that immunological dysregulation was considerably influenced by gut barrier failure. These results imply that immunological disruptions in COVID-19 patients could be significantly influenced by gut microbiota dysbiosis and gut barrier dysfunction, which could exacerbate and accelerate the disease. One of the research's drawbacks is the very small sample size, which could restrict how far the results can be applied. Future research employing larger cohorts and longitudinal studies can provide more insight into the long-term consequences of gut barrier failure and microbial alterations in COVID-19 patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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