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ORIGINAL

Understanding the Relationship between Metabolome and Gut Microbiome in Acute Obstructive Pulmonary Disease and development of lung cancer risks

Comprensión de la relación entre el metaboloma y la microbiota intestinal en la enfermedad pulmonar obstructiva aguda y el desarrollo de riesgos de cáncer de pulmón

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ABSTRACT

The gut-lung axis links dysbiosis of the gut microbiota to bronchiectasis. Gaining knowledge of the metabolic and microbiological changes can help one understand how a disease develops. To investigate at how the metabolome, gut microbiota, and bronchiectasis are related, and to find possible biomarkers for the diagnosis and treatment of disease was the aim of this research. 150 participants' fecal samples (42 Healthy Controls (HC), 48 Stable Patients (SP), and 60 Acute Exacerbation (AE)) were examined using LC-MS-based metabolomics and 16S rRNA sequencing. For statistical analysis, SPSS 19.0 were utilized, along with Pearson's correlation and LDA effect size (LEfSe). Microorganism diversity was reduced in bronchiectasis patients, with firmicutes and Bacteroidetes being less prevalent. There were changes in several metabolic pathways, such as the metabolism of glycerophospholipids, sphingolipids, purines, and tryptophan. Research emphasizes that the pathophysiology of bronchiectasis is influenced by the gut flora. The significance of more longitudinal research is highlighted by the potential diagnostic and therapeutic targets provided by identified microbial and metabolic biomarkers.

Keywords: Alternative Ingredients; Broilers; Lipid Peroxidation; Probiotics; Growth.

RESUMEN

El eje intestino-pulmón relaciona la disbiosis de la microbiota intestinal con la bronquiectasia. Conocer los cambios metabólicos y microbiológicos puede ayudar a comprender cómo se desarrolla una enfermedad. El objetivo de esta investigación era estudiar la relación entre el metaboloma, la microbiota intestinal y la bronquiectasia, y encontrar posibles biomarcadores para el diagnóstico y el tratamiento de la enfermedad. Se examinaron muestras fecales de 150 participantes (42 controles sanos [HC], 48 pacientes estables [SP] y 60 con exacerbación aguda [AE]) mediante metabolómica basada en LC-MS y secuenciación de ARN ribosómico 16S. Para el análisis estadístico se utilizó SPSS 19.0, junto con la correlación de Pearson y el tamaño del

efecto LDA (LEfSe). La diversidad de microorganismos se redujo en los pacientes con bronquiectasias, siendo menos prevalentes los firmicutes y los bacteroidetes. Se observaron cambios en varias vías metabólicas, como el metabolismo de los glicerofosfolípidos, los esfingolípidos, las purinas y el triptófano. La investigación destaca que la fisiopatología de la bronquiectasia está influenciada por la flora intestinal. La importancia de realizar más investigaciones longitudinales se pone de relieve por los posibles objetivos diagnósticos y terapéuticos que proporcionan los biomarcadores microbianos y metabólicos identificados.

Palabras clave: Ingredientes Alternativos; Pollos de Engorde; Peroxidación Lipídica; Probióticos; Crecimiento.

INTRODUCTION

The application of ribosomal ribonucleic acid (rRNA) gene-based amplicon over Chronic Obstructive Pulmonary Disease (COPD) micro-biome is done, to determine the Micro-biome's biological structure.[1] To investigate the functional aspects, only limited studies used meta-transcriptomic or meta-genomic sequencing techniques. While studies in the past few years have linked specific microbial metabolites to inflammation. The community-level airway micro-biome in COPD produces metabolites that affect host immunity.[2] The increasing accessibility of multi-omic on the Micro-biome and host presents a chance to integrate current understanding that reveals complex connections across an individual and their intestinal micro-biota.[3] The ability to expose consistent disease-associated micro-biome patterns on an unprecedented scale has been demonstrated using meta-analysis. It created a catalog of Micro-biome-metabolites and analyzed their molecular relationships with host targets.[4] Extended airway remodeling along with inflammation is the common and chronic illness known as COPD. Asthma, dyspnea, sputum production, prolonged cough and chest pain are significant clinical symptoms.[5] COPD is portrayed as the fourth largest cause of death globally, impacting around 400 million people. Due to the increased prevalence, significant social and economic costs, COPD is considered as a critical social issue.[6] Since there are less medicinal aids for COPD, it is critical to slow or stop its progression and lower death rates. The gut micro-biota is a dynamic ecological community composed of bacteria, archaea and protists coexisting in gastrointestinal tract.[7] The preservation of gut barrier function, homeostasis, digestion, metabolism and innate immunity, are actively regulated by microbial community. Gastrointestinal problems and related symptoms prevail with chronic respiratory conditions such as COPD, and respiratory virus infections.[8] An increasing amount of research shows a link between the development of lung disorders, modifications to gut microbial composition and activity known as the gut-lung axis. Thus, the reciprocal interaction is essential for regulating local cellular activity.[9] While in precise mechanisms, the correlation is based on patients with reduced lung function combined with gut micro-biota and influenza patients experiencing gastrointestinal symptoms. The necessity to investigate the association and potential therapeutic approaches between COPD and the gut micro-biota is highlighted by the growing understanding of interaction.[10] It explored the intricate relationships of the micro-biota of the intestines, its metabolic products coupled with COPD, combining the variables affecting the axis connecting the stomach, lungs and the gut micro-biome.

COPD, a lung disease characterized by permanent airflow blockage, was increasing in frequency, raising global health concerns due to factors namely smoking, environmental and occupational factors. The symptom presentation and functional restriction severity resulted in a delayed diagnosis was discussed in the article.[11] Significant healthcare use and expenses were associated with morbidity related to COPD. Article [12] provided a thorough analysis of the epidemiology, pathophysiology, diagnosis including treatment of COPD, exposing the difficulties faced by medical professionals and patients in tackling the widespread of COPD worldwide as health issue. The COPD analysis was employed[13] to detect relationships that exist between the host and the airway microbiology were yet unknown. The prediction of operational features of COPD lung Micro-biome was also performed and utilized a thorough multi-omic meta-analysis technique. Research [14] used 12 microbial genera as the basis for COPD. It was discovered microbial taxonomic alterations through a meta-analysis of random impacts. The lung micro-biome's physiological capacity was implemented [15] which assessed the chemical relationships to maintain values and examined their effects. It was performedafter using 1340 publicly available human airway transcriptomic samples for COPD in a different meta-analysis. Interestingly, Micro-biome metabolism was expected to affect 29,6 % of human pathways that were expressed [16] An evaluation of multi-omic research including COPD patients and controls was performed, to evaluate the harmonic reaction involved COPD ecology in patients.[17] It was identified by examining predicted metabolite–host interactions andit included airway metagenomic, host transcriptomic and Metabolome studies. Research [18] used three microbial metabolites that comprisedof highest interactions with host genes linked with COPD known as butyrate, homocysteine and palmitate. Article [19] introduced the functional characteristics of the respiratory ecosystem that impact COPD host gene profiles and revealed the outcomes by using meta-analysis. It highlighted

the possibility of using publicly available multi-omic data to investigate the biology of the disease. Work [20] addressed inconsiderate clinical pathways, gut dysfunction in individuals and implications in respiratory illnesses show gut-lung exchange. With increased gut permeability, gut bacteria present in acute lung diseases namely, sepsis yet trauma enrich the lung micro-biota, cause inflammation,and damage.

Article [21] examined the gut-lung axis in relation to Inflammatory Bowel Disease (IBD) and COPD, emphasizing the critical role that microbial dysbiosis plays as well as the influence of genetic and environmental factors on the innate and acquired immune systems and chronic inflammation in the intestinal and pulmonary tracts.An estimate for investigating the mechanism of COPD and potential biomarkers for clinical diagnosis and treatment may be offered by this analysis.[22] The analysis [23] explored into the connection between the severity of COPD and gut microbiome. This research shows no discernible relationship between any specific gut microbiota pattern and the severity of COPD. By influencing the human immune system through gut inflammation, the gut microbiota could have an impact on COPD. To assessed the correlations between disease symptoms and repeatable characteristics of the airway bacterial interactome in COPD during exacerbations and during clinical stability was the aim of this article.[24]

The aim of the research is to examine the connection between the metabolome and gut microbiota in individuals suffering from Acute Obstructive Pulmonary Disease (AOPD). It uses LC-MS and 16S rRNA sequencing to investigate metabolic changes, identify bacterial taxa associated with disease, and evaluate microbial diversity. It also investigates the gut-lung axis in an effort to find possible AOPD biomarkers and treatment targets.

METHOD

Data collection

60 patients with acute exacerbation bronchiectasis (AE), 48 patients with stable phase bronchiectasis (SP), and 42 healthy controls (HC) represented the research's 150 participants. Fecal samples were obtained from the subjects in order to investigate the metabolome using liquid chromatography-mass spectrometry (LC-MS) and the microbiome using 16S rRNA sequencing. Clinical information such as Forced Expiratory Volume (FEV1), antibiotic use, and smoking status were documented. Table 1 presents the characteristics that pertain to the group which was exposed.

Table 1. The investigative individual's characteristics

Variables	Healthy Controls (HC) (n=42)	Stable Phase (SP) (n=48)	Acute Exacerbation (AE)(n=60)
	Gender		
Male	24	26	34
Female	18	22	26
	Smoking Status		
Never Smoker	27	20	22
Ever Smoker	15	28	38
	Medication		
Oral/IV antibiotics	0	18	22
Fev1 % Predicted	42	30	38
	P.aeruginosa infection		
Yes	0	20	38
No	42	28	22

Gut Microbiome Identification

To identify between different medical disorders, the gut microbiome must be identified by examining microbial patterns. Significant microbial alterations can be revealed by comprehending non-linear correlations in biological data. Based on their correlation with illness states, several genera were chosen for this investigation as possible biomarkers. The results provide crucial insight into the role of the gut microbiota in the onset of illness and its potential as a diagnostic tool.

Metabolism Data Analysis for SP and HC using LC-MS Platform

The methodologies that were discussed above were used to carry out metabolite profiling on fecal blood samples. Using an ethylene bridged hybrid (BEH) ultra-performance liquid chromatography (UPLC) amide column, a high resolution accurate (HFX) mass spectral was coupled to a Vanquish ultra-high (UHPLC) system. The concentration of ammonia hydroxide and ammonium acetate in the ocean (A) was 24mmol/L, whereas the concentration in acetonitrile (B) was the same. During the gradient elution, thirty degrees Celsius was the

constant temperature in the column. A Thermo Q Thermo-activated mass spectrum HFX was able to get spectra while in the Information-Dependent Acquisition (IDA) mode with the use of Xcalibur software. Extraction of data, alignment of data, integration of data and identification of highlights were conducted.

Analytical statistics

The Levine test was used to evaluate the clinical variables that differentiated the groups. To analyze correlations, Pearson's correlations were used. The SPSSversion 19.0 for Windows was used to conduct statistical analysis.The LDA effect size (LEfSe) method was applied in conjunction with an LDA score of more than 2 and the Wilcox on rank-sum examination (P < 0,04), to characterize the bacteria that are present in faces. To discover changes in fecal chemicals, this research used T-tests with two tails for students (P value less than 0,04). Additionally, variable importance in projection (VIP less than 1) was implied, to assess statistical significance. Further, Spearman's correlation analysis was used to assess correlations.

RESULT

Reduced Variety of Gut Microbes in Bronchiectasis

A total of 4 761 541 readings of outstanding quality were obtained, producing a mean number of 48 860 for each sample. With 79, 21 and 15 OTUs, which are unique to the respective HC, SP and AE categories, comparison research revealed that there were 156 and 211 OTUs that discriminated between HC-SP and HC-AE. According to the diversity metric, patients who were diagnosed with bronchiectasis had decreased levels of microbial richness and diversity. By using Principal Coordinate Analysis (PCoA), it was able to establish the various microbial community distributions seen in faces and these findings were verified repeatedly using comparisons.

Alterations in the facial microbiota connected to bronchiectasis

The most common groups were analyzed at the various tiers of genus and groups using microbial tax on assignment. In HC and SP categories, Firmicutes were the most prevalent organisms, accounting for 60,2 % and 57,0 % of all OTUs. Bacteroidetes predominated in the AE group, demonstrates an increased percentage and revealed a lower Firmicutes/Bacteroidetes ratio in bronchiectasis. The HC group possesses a higher proportion of Bacteroidetes. The number of proteobacteria increased in AE, whereas it decreased in SP when compared to HC. The genus-level analysis of the AE and SP groups revealed the presence of 23 and 50 different altered genera and these findings exhibited relationships with clinical indicators. Microorganisms are broken down into their respective taxonomic groupingsas shown in table 2 and figure 1. The categorization of microbiological taxonomic groupings is deliberated in table 3 and figure 2.

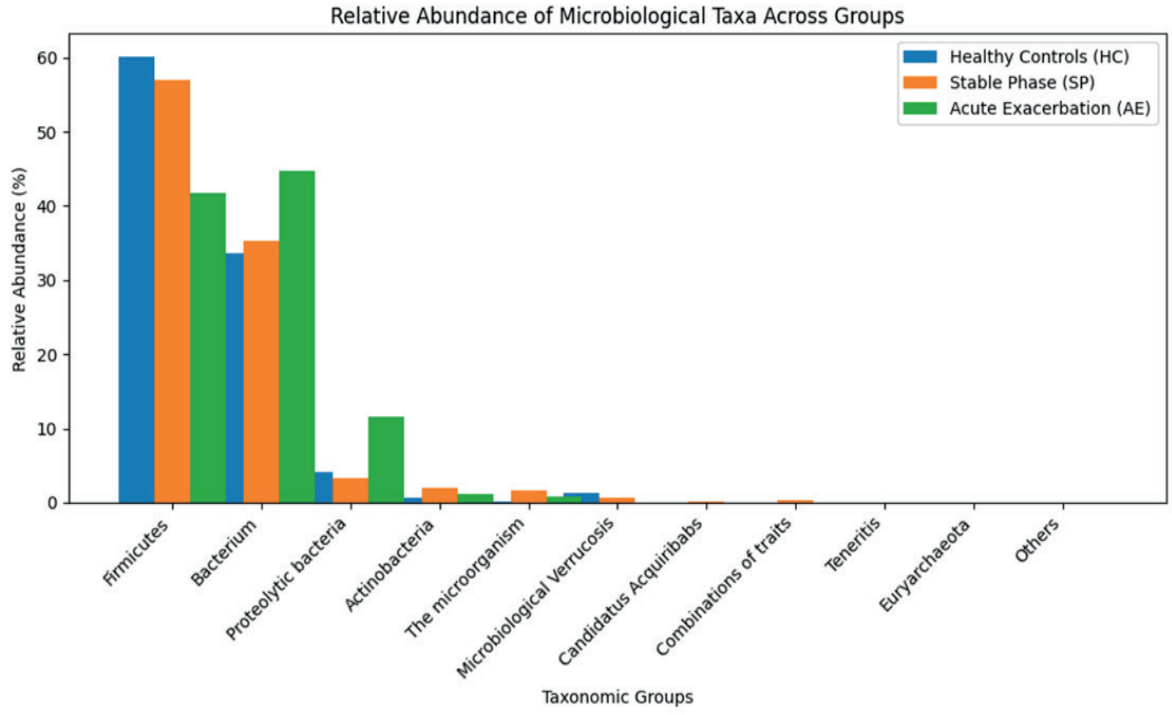

Figure 1. Relative Abundance of Microbiological Taxa Across Groups

Table 2. Separating Microbiological Taxa Categories			
Taxonomy	**Relative abundance (%)**		
	HC	**SP**	**AE**
Bacteria Firmicutes	60,20518	56,96727	41,73801
Bacterium	33,58957	35,270104	44,78217
Proteolytic bacteria	4,093003	3,270104	11,50887
Acrtionobacterria	0,67343	1,976264	1,085493
The microorganism	0,157838	1,634370	0,782303
Microbiological Verrucosis	1,254197	0,72701	0,034815
Candidatus Acquiribabs	0,007895	0,15128	0,027805
Combinations of traits	0,015007	0,23820	0,00295
Teneritis	0	0	0,03083
Euryarchaeota	0,002936	0	0,004516
Others	0	0	0

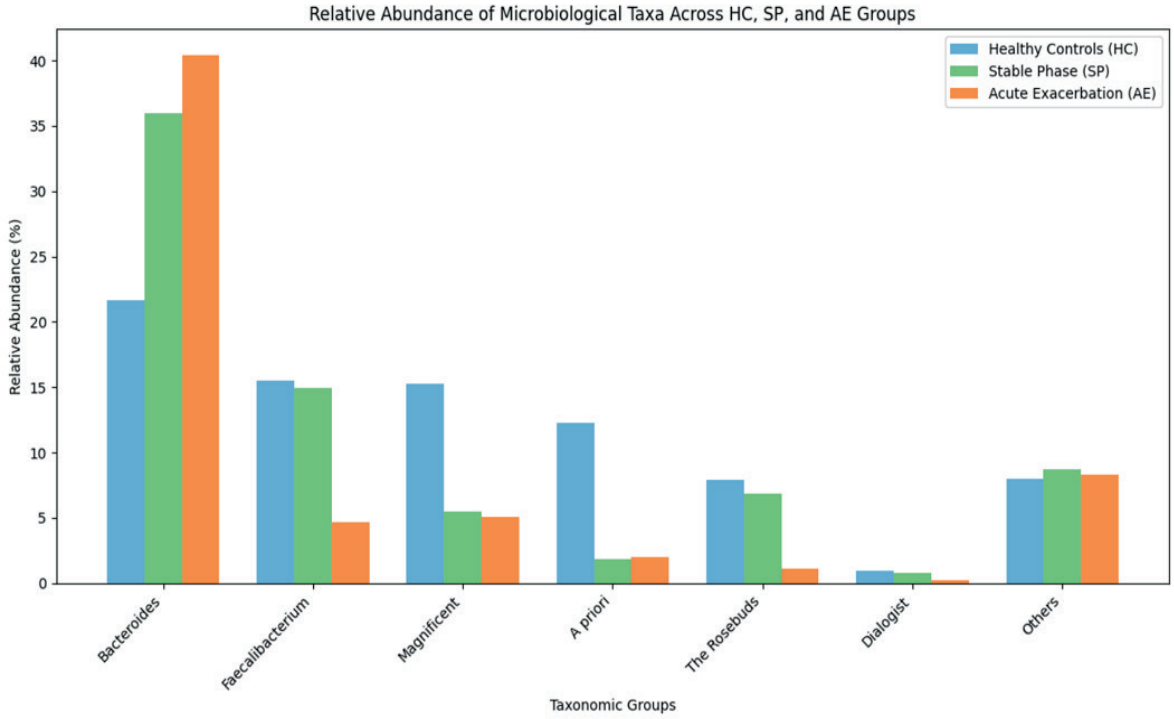

Figure 2. Group-Wise Microbial Taxa Abundance comparison

Table 3.Sorting Microbiological Taxa Groups			
Taxonomy	**Relative abundance (%)**		
	HC	**SP**	**AE**
Bacteroides	21,67716	35,93592	40,38238
Faecalibacterium	15,46444	14,94367	4,66680
Magnificent	15,25626	5,46994	5,094742
A priori	12,27403	1,807048	2,016402
The Rosebuds	7,91841	6,835605	1,112314
Dialogist	0,960110	0,824288	0,259023
Others	7,985738	8,746023	8,324405

The functioning of the gut microbiota in patients having bronchiectasis

The 16S rRNA is a gene sequencing method, which was deployed in suggested research, investigating clusters by reconstructing and LEfSe analysis in their multimodal strategy to research the gut micro-biota of patients with bronchiectasis. The purpose of all theseencompassing approaches was to identify functional shifts in the bacterial community. Significant alterations were found in the AE, SP and HC groups, accounting for 96, 34 and 62 pathways, respectively, out of 400 MetaCyc pathways analyzed. A strong statistical model with an LDA

scores of 1 and a significance level of P < 0,04 supported these results. The major strength is the capacity of the method to forecast functional modifications in microbiota of gut and exposing key highlights into putative pathways underlying pathophysiology. Even with these insightful discoveries, it is crucial to recognize certain drawbacks, such as the research's cross-sectional design, which calls for further in-depth research. Moreover, extending the research to include supplementary omic data and considering the impact of tailored therapies couldimprove the comprehensiveness and relevance of future investigations. This helps in managing and comprehending dysbiosis associated with bronchiectasis.

Based on Gut Microbial Genera, SP Patient's Identification and Validation

In developing the model as well as performing Metabolome studies, the research examined samples from SP and HC. It was able to reduce the possible effects of recent antibiotic use on the bacteria in the intestines coupled with metabolites in the AE group. The distribution of the fecal micro-biota that LEfSe had detected shown graphically using a Cladogram, which highlighted the taxonomic distinctions between the HC and SP groups. Superior discriminative power was shown by the top 10 genera, including Prevotella and Bifidobacterium (AUC: 0,936). An independent validation cohort further supported these findings, demonstrating the robustness of the outcomes (AUC: 0,867). The purpose of this deliberate removal of AE samples was to improve the accuracy of the research's identification of gut microbial biomarkers linked to bronchiectasis. It is done by separating the distinct influence of the condition from the potentially confusing effects of recent antibiotic use. The confirmation of findings in a separate cohort exposes the potential usefulness of the developed genera as markers in differentiating people with bronchiectasis and lends credence to the observed discriminating ability of the genera.

Patients with bronchiectasis have altered fecal Metabolome

Research examined the relationship between gut micro-biota and gut physiology of individuals with bronchiectasis, considering the correlation between dysregulated micro-biota and the condition. Chemicals were found using a non-targeted LC-mass spectrometry (LC-MS)-based on metabolomics technique. OPLS-DA plot of scores revealed a clear distinction between the HC and SP groups as a result of the research, which identified 44 abundant metabolites in SPs. Significant differences in the purine, tryptophan, glycerophospholipid and sphingolipid metabolic pathways were shown by altered metabolites, such as adenosine and lactosylceramide, in the SP group. This thorough investigation in detecting the relationship between the gut micro-biota and Metabolome illuminates putative metabolic markers and pathways linked to bronchiectasis. Italsoprovides new significantinformation for future studies and possible treatments to modify patient's dysregulated gut micro-biota.

DISCUSSION

The outcomes of this research provide important new information on the patho-physiology of bronchiectasis by illuminating notable metabolic and microbiological changes in the guts of affected individuals. The predominance of Bacteroidetes along with the observed decline in microbial diversity and richness in bronchiectasis patients point to a unique gut micro-biota composition linked with illness. Moreover, different metabolic pathways associated with bronchiectasis are revealed by the thorough multi-omic research. These pathways include modifications to the metabolism of purine, tryptophan, glycerophospholipid and sphingolipid. Thus, the changes provide possible targets for therapeutic therapists to correct the dysregulated gut micro-biota in those individuals having bronchiectasis. In spite of these insightful findings,the researchdivulges the need for increased long-term research while acknowledging limitations of cross-sectional methodology. Furthermore, the removal of AE samples from the identification and validation of gut microbial biomarkers is intended to improve accuracy, but it is important to take possible antibiotic side effects into account. By considering all the aspects, this researchlays the groundwork for future research into customized treatments and enhanced clinical outcomes by illuminating the complex interactions among the gut micro-biota, Metabolome and bronchiectasis.

CONCLUSION

Finally, a thorough multi-omic investigation reveals new details on the pathogenesis of bronchiectasis by illuminating the intricate connection between gut bacteria and the disease. It is possible that bronchiectasis patients have a unique microbial signature because of the decreased microbial diversity, changed compositions, and especially with the predominance of Bacteroidetes. The capacity of particular genera, including Prevotella and Bifidobacterium, to differentiate across various conditions highlights their usefulness as diagnostic markers. Furthermore, the relevance of the gut Metabolome in bronchiectasis is shown by the detection of 44 differentially abundant metabolites and changes in the tryptophan, glycerophospholipid, purine and sphingolipid pathways. The strength of the suggested researchis its integrated methodology, which makes use of LC-MS metabolomics and 16S rRNA sequencing is backed by statistical models. By altering the dysregulated gut micro-biome, the

findings not only advanced knowledge of bronchiectasis, but also suggested potential treatment interventions. Nevertheless, the researchacknowledgedits drawback of cross-sectional design and need for more thorough investigation. Subsequent studies that incorporate more omic data and take customized treatments into account could potentially understand dysbiosis in bronchiectasis and lead to better therapeutic outcomes. Overall, this research indicates health analysis by providing new insights into the potential treatment and diagnosis functions performed by the intestinal micro-biota and metabolism in bronchiectasis. The dynamic alterations in the gut micro-biota and the pattern of energy over time in bronchiectasis should be investigated in future studies, to clarify longitudinal trends and identify possible treatment approaches. This research's cross-sectional approach calls for more longitudinal research, to determine causal links and enhance the research comprehension of the temporal dynamics of gut-micro-biota interactions in bronchiectasis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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