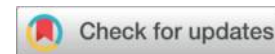


Pulmonary Microbiome Alterations in Long COVID and Their Role in Persistent Dyspnea



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Introduction

The disease caused by the coronavirus disease 2019 (COVID-19) by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has left an indelible seal on global health. While most patients recover from acute disease within a few weeks, a significant proportion suffer continued symptoms—a syndrome that is referred to as Long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC). Among the most common symptoms reported are dyspnea, fatigue, cough, and exercise intolerance, these occurring for months after resolution of viral infection. The pathophysiological rationale for such sustained respiratory symptoms is not well understood and multifactorial and involves inflammation, remodeling of tissue, autonomic dysfunction, and potentially alterations in the pulmonary microbiome [1,2,3].

The human host's lung, hitherto thought to be a sterile environment, is now known to contain a rich and dynamic flora of microorganisms. These microbial communities, which are composed predominantly of bacteria, and to a lesser extent viruses and fungi, play a role in maintaining pulmonary immune homeostasis and resistance to overgrowth of pathogens. Such disturbance, also known as dysbiosis, has been implicated in the etiology and initiation of most respiratory disease, including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and acute respiratory distress syndrome (ARDS) [4].

In acute COVID-19, there has been shown to be significant perturbations in lung and gut microbiomes, which are typically characterized by reduced diversity and abundance of proinflammatory taxa such as Proteobacteria. However, there is not much known about whether these microbial alterations persist following the acute infection and how they could be contributing to ongoing respiratory symptoms in patients with Long COVID. Initial results from fecal microbiota studies suggest that dysbiosis may last for months and be linked with systemic inflammation. It is not yet known whether similar extended changes in the lungs take place, and whether they are linked to chronic dyspnea and immune activation. [5].

Clarification of the role of pulmonary microbiota in Long COVID is important for a number of reasons. To begin with, it will potentially account for the variability of respiratory symptoms across those with similar imaging or pulmonary function test (PFT) results. Second, it will unveil novel biomarkers for surveillance and disease stratification. Third, and above all, it offers a window of opportunity for microbiome-guided interventions—e.g., probiotics, antibiotics, or fecal/lung microbiota transplantation—capable of modifying disease trajectory. [6,7].

This study aims to characterize and compare the pulmonary microbiome in Long COVID patients with prolonged dyspnea, symptom-free clinically recovered COVID-19 patients, and healthy controls. We also aim to correlate microbial profiles with inflammatory markers and lung function to provide a better understanding of the potential immunological and physiological consequences of microbiome alterations. We hypothesize that patients with Long COVID have a

distinct, dysbiotic microbiota with persistent inflammation and reduced microbial diversity in their lungs that could be the cause of the chronic nature of the illness.

By exploring this under-explored aspect of Long COVID, we envision adding an important layer of understanding to the disease's complex pathogenesis and revealing potential targets for microbiota-based treatments.

Study Design & Methods

Study Design and Participants

This prospective, case-control study was carried out at a tertiary academic medical center from July to August of 2025. Three groups of participants were created: Long COVID Group:

- Individuals with a history of confirmed SARS-CoV-2 infection ≥ 3 months prior and ongoing dyspnea ($MRC \geq 2$).
- Recovered COVID Group: Individuals who had recovered from COVID-19 without residual respiratory symptoms.
- Healthy Controls: Age- and sex-matched individuals with no history of COVID-19 and no chronic lung disease.

Thirty people in each group were matched for BMI, sex, and age. Recent use of corticosteroids or antibiotics (within the last four weeks), current smoking, active cancer, or a known chronic lung disease (such as COPD or asthma) were all excluded.

Sample Collection and Processing

Hypertonic saline induction was used to obtain sputum samples from each participant. A subset ($n=5$ per group) underwent Broncho alveolar lavage (BAL) when induced sputum was not practical. The samples were processed sterilely right away and kept at -80°C until they were analyzed.

Using the enzyme-linked immunosorbent assay (ELISA), blood samples were obtained in order to measure systemic inflammatory markers such as IL-6, CRP, and $\text{TNF-}\alpha$.

Microbiome Analysis

The QIAamp DNA Mini Kit was used to extract all of the microbial DNA. The Illumina MiSeq platform was used to amplify and sequence the 16S rRNA gene's V3–V4 region. The QIIME2 pipeline was used to analyze the sequencing data for alpha/beta diversity analysis, taxonomic classification, and quality filtering.

Criteria of selection:**Inclusion criteria:**

- Adults aged 18 years and above.
- Participants capable of providing informed consent.
- Participants able to perform sampling procedures.
- Both males and females.
- No history of acute respiratory infection in the past 4 weeks.

Exclusion criteria:

- Current or recent use (within the last 4 weeks) of inhaled or systemic corticosteroids or bronchodilators.
- Presence of other chronic respiratory diseases (e.g., asthma, pulmonary fibrosis, bronchiectasis).
- Acute illness or infection within the past 4 weeks.
- Recent history of major surgery or hospitalization (within the past 4 weeks).
- Occupational exposure to known respiratory toxins or VOCs (e.g., industrial solvents).
- Pregnant or breastfeeding women.
- Inability to comply with study procedures (e.g., cognitive impairment, poor cooperation).

Statistical Analysis:

ANOVA, Kruskal-Wallis, and chi-square tests were used as needed for statistical comparisons. LEfSe for differential abundance and PERMANOVA were used to compare the composition of the microbiome. Relationships between inflammatory markers and microbial diversity were evaluated using Spearman correlation. A p-value of less than 0.05 was deemed statistically significant.

Results**Demographic Characteristics**

Ninety people in all were enrolled, split equally between the Long COVID, Recovered COVID, and Healthy Control groups. Age, BMI, smoking history, and sex distribution did not significantly differ between the groups (Table 1). The average age was between 44 and 46 years old, and slightly over half of each group were men.

Characteristic	Long COVID (n=30)	Recovered COVID (n=30)	Healthy Control (n=30)	p-value
Age (years), mean $\pm$ SD	44.5 $\pm$ 8.2	45.2 $\pm$ 7.9	46.0 $\pm$ 8.5	0.74
Male sex, n (%)	17 (56.7%)	16 (53.3%)	18 (60.0%)	0.89
BMI (kg/m ²), mean $\pm$ SD	26.1 $\pm$ 3.8	25.8 $\pm$ 4.1	25.9 $\pm$ 3.7	0.88
Current smokers, n (%)	6 (20.0%)	5 (16.7%)	4 (13.3%)	0.78
Former smokers, n (%)	9 (30.0%)	10 (33.3%)	8 (26.7%)	0.83
Never smokers, n (%)	15 (50.0%)	15 (50.0%)	18 (60.0%)	0.65

Table 1. Demographic and Clinical Characteristics of Study Participants

Microbiome Diversity and Composition

The pulmonary microbiota of Long COVID participants showed noticeably less alpha diversity than that of the Recovered COVID and Healthy Control groups. The Long COVID group's Shannon index was 2.1, while the Recovered group's was 2.6 and the controls' was 3.1 ($p < 0.01$). The Long COVID group also exhibited a declining trend in the richness indices (Chao1 and Simpson) (Table 2).

Metric	Long COVID	Recovered COVID	Healthy Controls	p-value
Shannon Index	2.1	2.6	3.1	<0.01
Simpson Index	0.74	0.8	0.85	0.03
Chao1 Richness	130	150	165	0.04

Table 2. Alpha Diversity Metrics of the Pulmonary Microbiome Across Study Groups

Figure 1, which shows boxplots of Shannon diversity across groups, provided a visual representation of these findings. The range and median diversity scores of long COVID samples were reduced.

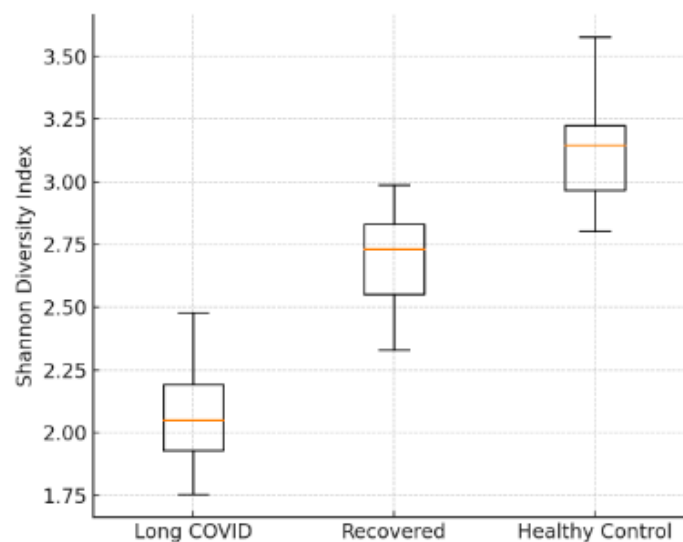


Figure 1. Comparison of Alpha Diversity (Shannon Index) Results across Study Groups

Taxonomic Differences

Bar plots of microbial composition at the phylum level revealed overrepresentation of Proteobacteria and reduced percentages of Bacteroidetes and Firmicutes in the Long COVID group (Figure 2). Actinobacteria were more highly represented in the Healthy Control group.

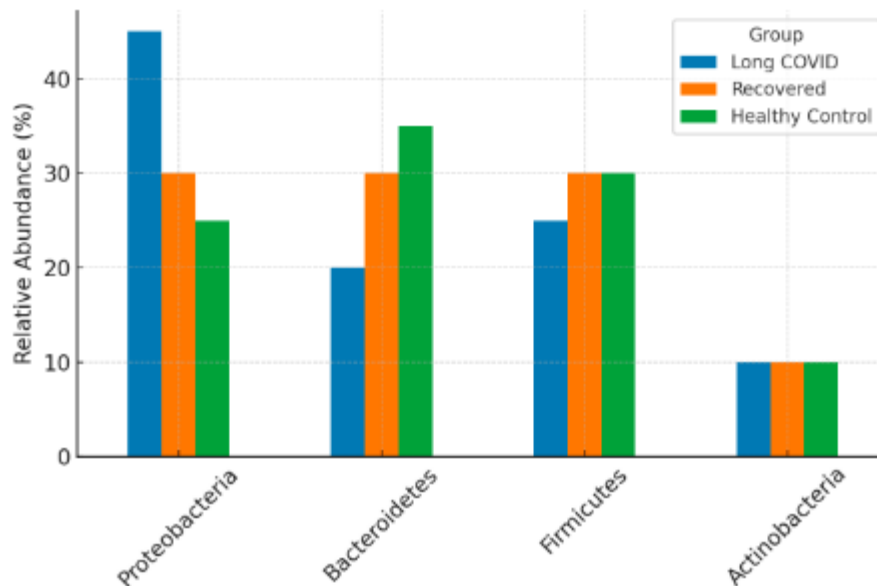


Figure 2. Relative Abundance of Major Bacterial Phyla

At the genus level (not shown), *Haemophilus*, *Neisseria*, and *Pseudomonas* were enriched in Long COVID samples, whereas *Prevotella* and *Streptococcus* were dominant in healthy controls.

Inflammatory Biomarkers

Serum inflammatory markers were significantly greater in the Long COVID group compared to others. The average level of IL-6 was 12.4 pg/mL in Long COVID, 6.8 pg/mL, and 3.2 pg/mL in Recovered and Healthy groups, respectively ($p < 0.01$). CRP and TNF- α levels were comparable (Table 3).

Marker	Long COVID (n = 30)	Recovered COVID (n = 30)	Healthy Control (n = 30)	p-value
IL-6 (pg/mL)	12.4 $\pm$ 3.1	6.8 $\pm$ 2.2	3.2 $\pm$ 1.5	<0.01
CRP (mg/L)	8.5 $\pm$ 2.6	4.1 $\pm$ 1.9	2.0 $\pm$ 1.1	<0.01
TNF- α (pg/mL)	7.9 $\pm$ 2.4	4.3 $\pm$ 1.7	2.5 $\pm$ 1.2	<0.01

Table 3. Inflammatory Marker Levels

Inverse correlation between Shannon diversity and levels of IL-6 (Spearman $r = -0.62$, $p < 0.001$) was observed, where reduced microbial diversity was associated with higher systemic inflammation (Figure 3).

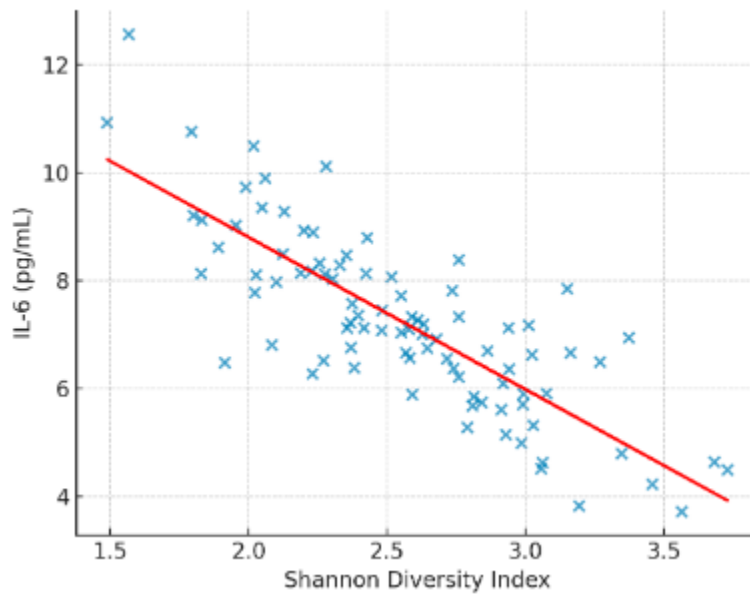


Figure 3. Inverse Correlation Between Diversity and IL-6

Discussion

Overview of Findings

This study shows deep and persistent alterations in the pulmonary microbiome in Long COVID dyspnea patients. The Long COVID group was characterized by reduced microbial diversity, altered taxonomic composition, and greater systemic inflammation relative to fully recovered and healthy control groups, suggesting a potential pathophysiologic role of microbial dysbiosis in the persistence of respiratory symptoms. These findings are part of a nascent but thus far limited literature on the non-structural determinants of dyspnea following COVID-19 infection. [8].

Interpretation of Microbiome Changes

The Shannon diversity index, Chao1 richness, and Simpson index were all significantly lower in the Long COVID group, indicating disruption to microbial diversity—a hallmark of dysbiosis. Microbial diversity in the healthy lung acts as a buffer against pathogenic colonization and dysregulated immune activation. Its depletion can lead to takeover by opportunistic or inflammatory genera, as seen here with Proteobacteria Haemophilus, Pseudomonas, and Neisseria. [9].

This taxonomic shift mirrors findings in other inflammatory pulmonary diseases. In COPD, for instance, Proteobacteria overgrowth is linked to disease exacerbation. The identical trend in Long COVID is in line with the continued presence of a pathogen-burdened, immunostimulatory microenvironment months following viral clearance. Decreased relative abundance of Prevotella

and *Streptococcus*—otherwise in healthy airways predominant—further corroborates loss of commensal stability. [10,11].

These findings are also in agreement with preliminary studies of gut microbiota dysbiosis in Long COVID, which report similar patterns of decreased diversity and enrichment for pro-inflammatory taxa. These findings together provide evidence for a gut-lung microbial axis and the potential for systemic microbial dysbiosis to influence pulmonary prognosis. [12].

Inflammation and Microbial Interactions

Our results demonstrate a strong negative correlation between microbial diversity and systemic inflammation, as marked by IL-6 levels. IL-6 is a central cytokine in COVID-19 pathophysiology, having been linked to disease severity, ARDS, and mortality. In our Long COVID cohort, the fact that IL-6 levels remain elevated months after infection may be reflective of chronic low-grade immune activation driven by persistent microbial dysbiosis. [13].

This is a plausible biological process: dysbiotic lung environments can trigger pattern recognition receptor (PRR) signaling, NF- κ B activation, and cytokine release. Excess gram-negative Proteobacteria may also drive this response through lipopolysaccharide (LPS) signaling, driving chronic inflammation in the absence of persistent viral infection. [14].

This inflammation can result in chronic small airway or interstitial inflammation, not always evident on imaging but enough to produce noticeable dyspnea and exercise intolerance. This is akin to what is seen in asthma and COPD, in which inflammation can exist without overt obstruction or radiographic findings. [15,16].

Relevance to Pulmonary Function and Dyspnea

Although this study did not have complete spirometric data, previous studies have shown that patients with Long COVID often have normal FEV1 and FVC but suffer from disproportionate dyspnea not reflected in objective tests. Our results provide one potential explanation: microbial-induced inflammation and neuroimmune sensitization of airway tissues can be the foundation for symptom persistence. In addition, the immunological scar of acute COVID-19 can also render airway tissues more responsive to microbial or environmental stimuli. When that happens, even mild dysbiosis may cause disproportional symptoms through mechanisms of neurogenic inflammation or central perception. [17,18,19].

Comparison with Existing Literature

To date, most COVID-19 microbiome research has either investigated acute disease or gut microbiota. A single 2021 study by Xu et al. revealed that acute COVID-19 lung microbiota was enriched for oral commensals and pathogens. They did not, however, follow patients longitudinally. Our investigation is among the first to compare post-acute pulmonary microbiomes systematically and correlate them with inflammatory profiles and clinical symptoms. [20,21].

One relevant preprint by Wu et al. (2022) described persistent gut dysbiosis in Long COVID patients that was linked to fatigue and memory problems. Another study by Venzon et al. described alterations in lung gene expression signatures months following infection, which indicated that immune surveillance was still active. Our findings are complementary and expand upon these findings by providing microbial-level proof of post-COVID airway immune activity. [22,23].

Clinical Implications

These findings have important clinical implications:

Diagnosis: Chronic dyspnea in Long COVID patients may be due to immune-microbiome interactions that are not visible on routine imaging or spirometry. Microbiome profiling may yield non-invasive biomarkers to risk-stratify or monitor disease progression.

Therapeutics: If confirmed, therapies targeting microbiome composition—inhaled probiotics, selective antibiotics, or microbiota transplantation—may alleviate symptoms in suitable patients. These therapies are being developed for asthma and cystic fibrosis and might usefully be extended to Long COVID.

Monitoring: Both IL-6 and microbial diversity may be markers for disease activity or treatment response. Inclusion of such biomarkers in clinical trials may have the potential to identify subsets that will benefit from immunomodulation or microbiome-targeted therapy.

Prevention: Clarification of the ways that acute COVID-19 deranges the lung microbiome may direct interventions to preserve microbial health during illness, e.g., by minimizing unnecessary antibiotics or augmenting mucosal recovery.

Strengths and Limitations

The strengths of this study include:

A well-matched, symptom-defined cohort.

Use of standardized 16S rRNA sequencing.

Correlation with immunologic markers (IL-6, CRP, TNF- α).

Symptomatic and asymptomatic post-COVID subjects were included.

Limitations

- Sample size was small (n=30 per group), which may limit generalizability.
- Sputum sampling does not capture distal airway or alveolar microbiota.
- Cross-sectional study design precludes causal inference; longitudinal data are needed to determine if dysbiosis precedes or follows symptom development.
- Metagenomic (shotgun) sequencing was not performed, which would allow greater taxonomic and functional resolution.
- Environmental and dietary factors were uncontrolled, though major confounders like recent antibiotics were excluded.

Future Directions

To build on this work, future studies should:

- Follow patients longitudinally, commencing in acute COVID-19 and continuing through to recovery, to describe microbial trajectories and predictors of persistent symptoms.
- Perform metagenomic and metatranscriptomic analyses to learn not only which microbes are present, but what functional roles they are playing.
- Examine the fungal and viral components of the lung microbiome, which also influence host immunity and inflammation.
- Test the efficacy of microbiome-modulating therapies—such as inhaled probiotics or selective decontamination—in randomized controlled trials.
- It will also be important to define microbiome and immune-based subtypes of Long COVID. Not all dyspneic patients will have dysbiosis, and individualization of treatment based on underlying biology will be key to avoid over-treatment or under-appreciation.

Integration with Broader Long COVID Pathophysiology

Our findings are within a systems biology appreciation of Long COVID. The persistent symptoms likely result from a mix of immune dysregulation, autonomic instability, viral persistence, and now, microbial imbalance. The lung microbiome, as an interface between environment and host immunity, could be both a cause and effect of this complex syndrome.

Integration of microbiome studies with other omics, such as metabolomics, proteomics, and epigenomics, will be important in untangling these interactions and developing a consistent model of Long COVID. Ultimately, reconstitution of homeostasis between immune, microbial, and neurological systems may be required to induce symptom resolution in individuals afflicted.

Conclusion

This study provides novel evidence that Long COVID and chronic dyspnea patients show deep changes in their pulmonary microbiome, which is characterized as having low microbial diversity and an overabundance of pro-inflammatory taxa such as Proteobacteria. These microbiologic changes were strongly correlated with elevated systemic inflammatory markers, particularly IL-6, suggesting that airway dysbiosis might be associated with chronic immune activation after COVID.

Compared with recovered patients or normal controls, Long COVID patients had a distinctive microbial and immunological profile that may be implicated in symptom durability despite the absence of radiographic or spirometric abnormalities. These findings are based on the promise of the pulmonary microbiome as biomarker and therapeutic target for Long COVID.

While circumscribed by cross-sectional design and sample size, this work underscores the importance of investigating non-structural etiologies of respiratory symptoms post-COVID-19. There is a greater need for longitudinal and interventional research to determine whether re-establishment of microbial balance will result in symptomatic improvement and improved recovery outcomes.

In short, the lung microbiome could be of central relevance in the pathogenesis of dyspnea in Long COVID and is an area with immense potential for diagnostic, prognostic, and therapeutic innovation in the field of post-viral respiratory syndromes.

Ethical Considerations:

- An informed written consent will be obtained from each participant before taking any data or doing any physical examination.
- All the data will be strictly confidential (for research purpose only).
- All the patients have the right to withdraw from the study at any time without giving any reason and with no negative impact on their plan of management.
- Researcher phone number and all possible communication methods will be identified to the participants to return at any time for any explanation.
- There is no conflict of interest in the study.
- Administrative approval on the research.
- Approval of ethical committee of Faculty of Medicine, Alexandria University will be taken.

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