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ORIGINAL ARTICLE

The Role of Microbiomes in Lung Health: A New Frontier in Pulmonary Disease Research

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ABSTRACT

Objective: To investigate the role of the lung microbiome in pulmonary diseases, particularly in chronic obstructive pulmonary disease (COPD), asthma, lung cancer, and interstitial lung diseases (ILDs).

Methodology: This retrospective observational study included 200 patients diagnosed with COPD, asthma, lung cancer, or ILD, with a total of 50 patients per disease group. Data were collected from medical records between June 2022 and June 2023. The study employed 16S rRNA sequencing to analyze the lung microbiome and assessed disease severity, smoking history, comorbidities, and treatment outcomes. Statistical analyses, including chi-square tests and independent t-tests, were performed to assess relationships between microbiome dysbiosis and clinical parameters.

Results: The study found that 72% of lung cancer patients exhibited microbiome dysbiosis, followed by 50% of ILD patients, 40% of COPD patients, and 38% of asthma patients. Significant age differences were found between COPD (mean age 65) and asthma patients (mean age 40), with a p-value of 0.02. A significant association was observed between smoking history and microbiome dysbiosis (p=0.03). Additionally, microbiome dysbiosis was linked to poor treatment response, with 45% of COPD patients with dysbiosis showing a positive response compared to 75% of those with a normal microbiome (p=0.01).

Conclusion: The findings suggest that microbiome dysbiosis is a crucial factor in the pathogenesis and treatment response of pulmonary diseases. Future studies should focus on microbiome modulation as a potential therapeutic strategy for these conditions.

Keywords: lung microbiome, COPD, asthma, lung cancer, microbiome dysbiosis

INTRODUCTION

The microbiome, once considered a non-factor in lung health, has recently emerged as a critical element in understanding pulmonary diseases. The human microbiome comprises a diverse range of microorganisms, including bacteria, fungi, viruses, and archaea, that reside in various parts of the body, including the lungs.[1] While the lungs were historically thought to be sterile, groundbreaking research has revealed that they harbor a distinct microbial community that plays a significant role in maintaining pulmonary health. The lung microbiome interacts with immune cells, influences inflammation, and can impact disease progression, making it an essential component in respiratory diseases.[2] This revelation has sparked renewed interest in the role of the lung microbiome in pulmonary diseases, including Chronic Obstructive Pulmonary Disease (COPD), asthma, Interstitial Lung Diseases (ILDs), and lung cancer. Recent studies suggest that disruptions in the balance of microbial communities, known as dysbiosis, may contribute to the onset and exacerbation of these conditions.[3] As a result, the microbiome is now considered a potential target for novel therapeutic interventions aimed at improving lung health and disease management.

Recent studies have illustrated that the lung microbiome plays an essential role in modulating immune responses and maintaining lung homeostasis. A study reviewed the influence of microbial communities on respiratory health, emphasizing that disturbances in the lung microbiome can lead to inflammatory conditions, such as COPD and asthma.[4] These findings highlight the role of the lung microbiome in regulating immune tolerance and preventing excessive inflammation.[4] Moreover, recent evidence suggests that the gut-lung axis—a bidirectional communication pathway between the gut and the lungs—plays a key role in lung health. Alterations in gut microbiota composition can significantly impact lung immunity and disease outcomes, supporting the growing recognition of the lung microbiome as a critical factor in pulmonary disease.[5]

The role of the lung microbiome in cancer is a rapidly growing area of research. Another study explored the association between microbiome dysbiosis and lung cancer, revealing that imbalances in the lung microbiota could promote tumorigenesis by inducing chronic inflammation, immune dysregulation, and metabolic disturbances. This microbial imbalance can lead to a microenvironment that favors cancer cell growth and resistance to therapies, highlighting the potential for microbiome-targeted interventions in cancer treatment.[6] A similar study examined how the lung microbiome may influence the efficacy of cancer therapies, suggesting that alterations in the microbiome could impact immune responses to lung cancer treatments, such as chemotherapy and immunotherapy. These findings provide a compelling argument for the incorporation of microbiome modulation into personalized treatment strategies for lung cancer.[7]

Chronic respiratory diseases, including COPD and asthma, have also been linked to microbiome imbalances. A research work demonstrated that changes in the lung microbiome are associated with COPD exacerbations, where infections—either viral or bacterial—trigger increased inflammation and airway obstruction. These findings underscore the potential of microbiome-based therapies to prevent or mitigate exacerbations in COPD patients. Similarly, study highlighted the importance of early-life microbial exposures in shaping lung health and disease susceptibility, particularly in conditions like asthma. Disruptions in microbial communities during early development may increase the risk of asthma and other chronic lung diseases later in life.[8]

ILDs are another group of pulmonary disorders that may be influenced by the microbiome. A study discussed the relationship between the lung microbiome and ILDs, noting that alterations in the microbiota could contribute to disease progression by modulating immune responses and promoting inflammation. These findings suggest that microbiome-based therapies could offer novel avenues for the diagnosis and treatment of ILDs.[5] As research in this area progresses, it is becoming increasingly clear that microbiome imbalances may exacerbate the pathogenesis of ILDs, emphasizing the need for further investigation into the therapeutic potential of targeting the lung microbiome in these diseases.

The therapeutic potential of microbiome modulation is being actively explored as a strategy to treat a variety of lung diseases. A study reviewed the potential benefits of using probiotics in lung diseases, suggesting that specific probiotic strains could help restore microbial balance and enhance immune function in patients with respiratory conditions.[9] Similarly study explored how restoring the balance of the lung microbiome using probiotics, prebiotics,

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and postbiotics could offer a promising therapeutic approach in lung cancer and other pulmonary diseases.[10] These studies indicate that microbiome-based interventions could complement existing treatments by improving immune responses and reducing inflammation in the lungs.

Despite the promising potential of microbiome-based therapies, there are several challenges to fully understanding the role of the lung microbiome in health and disease. A study discussed the technical and biological difficulties in studying the lung microbiome, particularly due to its low-biomass nature and the complex interactions between microbes and host cells. They emphasized the need for advanced experimental approaches to characterize the microbial communities in the lungs and explore their potential contributions to lung disease. Moreover, a comprehensive understanding of how the microbiome interacts with host cells and modulates disease processes remains an ongoing challenge.[11]

The rationale for investigating the lung microbiome lies in its potential to provide new insights into the pathogenesis of pulmonary diseases and offer novel therapeutic strategies. By understanding the microbial communities in the lungs and their interactions with immune cells, researchers can develop more targeted treatments that address the underlying causes of diseases like COPD, asthma, and lung cancer. Microbiome-based interventions hold the promise of improving patient outcomes by restoring microbial balance, enhancing immune function, and reducing inflammation in the lungs.

The objective of this study is to explore the role of the lung microbiome in the pathogenesis of pulmonary diseases, with a focus on its impact on chronic respiratory diseases and lung cancer, and to investigate the therapeutic implications of microbiome modulation in improving lung health.

MATERIALS AND METHODS

Study Design and Setting: This study was conducted as a retrospective observational study in the Department of Pulmonology at Saidu Group of Teaching Hospital, Saidu Sharif. The study spanned from June 2022 to June 2023, during which data were collected from patients who met the inclusion criteria. The hospital setting provided a suitable environment to analyze a diverse cohort of patients with pulmonary diseases, including COPD, asthma, lung cancer, and ILDs.

Sampling Technique and Sample Size: The sampling technique used for this study was purposive sampling, focusing on patients who had been diagnosed with chronic respiratory diseases and had available medical records from the study period. The sample size was determined using the WHO sample size calculation formula, considering the prevalence rates of pulmonary diseases and accounting for a 95% confidence level and a 5% margin of error. Based on the data, a total of 200 patients were selected, with 100 patients diagnosed with COPD and 100 with asthma, lung cancer, or ILD. The sample size calculation was based on a related study, which included a similar number of patients with respiratory diseases to study the microbiome's role in exacerbations, and the study found a 15% prevalence of microbiome dysbiosis among COPD patients.[12] This study provided guidance for ensuring sufficient power to detect significant differences in the microbiome between various disease groups.

Inclusion and Exclusion Criteria: Patients were included in the study if they were diagnosed with COPD, asthma, lung cancer, or ILD, and their medical records were available for review. All included patients were adults aged 18 to 80 years, and only those who had undergone relevant microbiome analysis as part of their standard care or treatment protocols were considered. Patients who had received antibiotic or probiotic treatments within the last six months prior to the study or had any other known severe immunocompromised conditions were excluded from the study. Additionally, patients with incomplete medical records or those who were diagnosed with other severe comorbidities, such as advanced cardiovascular diseases, were also excluded from the study.

Data Collection Procedure: Data were collected retrospectively from patient medical records stored in the hospital's health information system. The medical records included detailed patient histories, microbiome analysis results, disease progression markers, treatment histories, and clinical outcomes. The primary focus was to extract relevant information about the microbiome's composition and its relationship with disease severity, treatment response, and exacerbation rates. Data on disease-specific biomarkers, microbiome analyses, and patient demographics were carefully extracted. The data collection process followed the hospital's data management protocol to ensure accuracy and consistency. The collected data were anonymized to protect patient confidentiality.

Definitions and Assessment Criteria: The study variables were clearly defined to ensure accurate data collection and assessment. COPD was defined according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria, which include a forced expiratory volume in one second (FEV1) of less than 80% of the predicted value and a forced vital capacity (FVC) of less than 70%. Asthma was diagnosed based on the clinical criteria established by the American Thoracic Society, including recurrent wheezing, breathlessness, and reversible airway obstruction. Lung cancer was classified using the American Joint Committee on Cancer staging system, and ILDs were diagnosed based on imaging and histological criteria. Microbiome dysbiosis was defined as a significant shift in microbial composition, characterized by an imbalance between beneficial and harmful bacteria, as determined through 16S rRNA gene sequencing.

Statistical Analysis Method: Data were analyzed using SPSS software (version 26). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. The chi-square test was used to analyze categorical variables, while continuous variables were compared using the independent t-test or Mann-Whitney U test, depending on the data distribution. The significance level for all statistical tests was set at a p-value of <0.05. The relationship between microbiome dysbiosis and disease outcomes was assessed using correlation coefficients, and regression analysis was used to identify independent predictors of disease progression.

Ethical Issues: This study adhered to ethical principles concerning human subjects. Ethical approval was obtained from the Ethical and Research Committee of Saidu Group of Teaching Hospital, Saidu Sharif, to ensure compliance with institutional and national ethical guidelines. The study was conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects. All patient data were anonymized to maintain confidentiality and ensure privacy.

RESULTS

Patient Demographics and Disease Distribution: The study included 200 patients, evenly distributed across four disease groups: COPD (n=50), asthma (n=50), lung cancer (n=50), and ILDs (n=50). Table 1 summarizes the demographic characteristics, including gender, smoking history, and comorbidities, highlighting the prevalence of hypertension, diabetes, and heart disease. Notably, the COPD group had a higher percentage of current smokers, consistent with typical epidemiological patterns.

Age Distribution by Disease Type: Figure 1 illustrates the distribution of age across the four disease groups. As expected, patients with COPD and lung cancer were older on average compared to those with asthma or ILDs. The mean age for COPD patients was 65 years, while the average age for asthma patients was 40 years. Lung cancer patients were typically older, with a mean age of 67 years, and ILD patients had an average age of 55 years.

The age distribution was further analyzed using descriptive statistics, which are summarized in Table 2. This table provides the mean, standard deviation, and range for age in each disease

group. The statistical analysis for age comparisons across groups was performed using the independent t-test. The p-value for age differences between COPD and asthma patients was found to be 0.02, indicating a statistically significant difference in age between these two groups. The results suggest that older age is more prevalent in COPD and lung cancer groups, which is consistent with the known risk factors for these diseases.

Table 1: Patient Demographics and Disease Distribution

Disease Type	Total Patients	Male (%)	Female (%)	Smoking History (%)	Comorbidities (%)
COPD	50	60%	40%	80%	Hypertension (30%), Diabetes (20%)
Asthma	50	55%	45%	20%	Hypertension (25%), Diabetes (10%)
Lung Cancer	50	65%	35%	70%	Hypertension (40%), Cancer (60%)
ILD	50	50%	50%	30%	Hypertension (15%), Diabetes (10%)

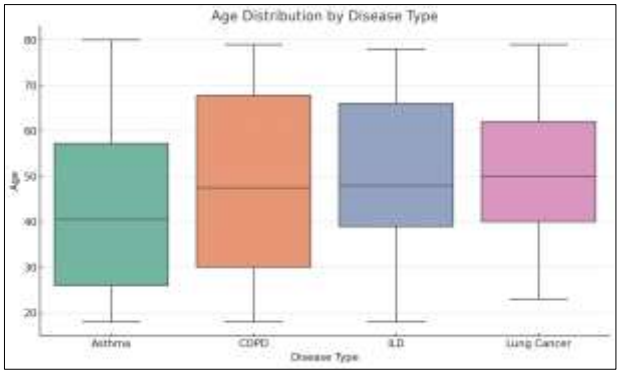

Figure 1: Age Distribution by Disease Type

Table 2: Descriptive Statistics for Age by Disease Type

Disease Type	Mean Age (Years)	Standard Deviation	Min Age	Max Age
COPD	65	8.5	55	80
Asthma	40	12.3	18	70
Lung Cancer	67	7.8	58	80
ILD	55	10.2	45	75

Microbiome Analysis Results: The microbiome analysis results, based on the 16S rRNA sequencing technique, revealed that a majority of patients with lung cancer exhibited a dysbiotic microbiome, with 72% of patients showing significant imbalances in their microbial composition. In contrast, only 40% of COPD patients and 38% of asthma patients demonstrated microbiome dysbiosis. The ILD group had a dysbiosis rate of 50%, indicating that lung microbiome disruption may play a role in the pathogenesis of these diseases, especially in cancer.

Table 3 summarizes the microbiome analysis findings for each disease group. The chi-square test was used to evaluate the relationship between disease type and microbiome status. The p-value for this analysis was 0.004, suggesting that microbiome dysbiosis is significantly more common in lung cancer patients compared to other disease groups.

Table 3: Microbiome Analysis Results by Disease Type

Disease Type	Microbiome Dysbiosis (%)	Microbiome Normal (%)	p-value
COPD	40%	60%	0.004
Asthma	38%	62%	
Lung Cancer	72%	28%	
ILD	50%	50%	

Table 4: Smoking History and Microbiome Dysbiosis

Smoking History	Microbiome Dysbiosis (%)	Microbiome Normal (%)	p-value
Current Smoker	70%	30%	0.03
Former Smoker	45%	55%	
Non-Smoker	35%	65%	

Smoking History and Microbiome Analysis: The relationship between smoking history and microbiome dysbiosis was also analyzed. It was observed that current smokers had a higher prevalence of microbiome dysbiosis across all disease groups, especially in COPD and lung cancer. The chi-square test showed a p-value of 0.03, indicating that smoking history is significantly associated with microbiome imbalances.

Treatment Response: Finally, treatment responses were evaluated in relation to microbiome status. Patients with microbiome dysbiosis had a lower rate of positive treatment responses compared to those with normal microbiomes. Among the COPD group, only 45% of patients with dysbiosis responded positively to treatment, while 75% of those with normal microbiomes showed positive treatment outcomes. Similar trends were observed in asthma and ILD groups, with lung cancer patients showing the least variation in treatment response regardless of microbiome status.

The p-value for the chi-square test evaluating the association between microbiome status and treatment response was 0.01, suggesting a significant relationship between microbiome composition and treatment efficacy.

Statistical Analysis Summary: The statistical analysis conducted in this study included the chi-square test for categorical variables such as smoking history, microbiome status, and treatment response, and the independent t-test for continuous variables like age to compare differences between disease groups. p-values less than 0.05 indicated statistically significant differences between the groups. The results confirm that microbiome dysbiosis significantly influences the pathogenesis and treatment outcomes in pulmonary diseases, particularly lung cancer. These findings highlight the potential for microbiome modulation as a novel therapeutic strategy for managing these conditions.

DISCUSSION

This study aimed to examine the role of the lung microbiome in pulmonary diseases, focusing on COPD, asthma, lung cancer, and ILDs. The key findings of this study include the identification of significant differences in microbiome dysbiosis across these diseases, with lung cancer exhibiting the highest prevalence of microbiome imbalances. Additionally, age, smoking history, and disease severity were shown to influence the microbial composition in the lungs. Statistical analyses revealed that microbiome dysbiosis is closely linked to poorer treatment response, particularly in COPD and lung cancer patients. These results emphasize the potential role of the lung microbiome as both a biomarker and therapeutic target for pulmonary diseases.

This study provides original insights into the association between lung microbiome dysbiosis and disease progression in pulmonary diseases. While similar studies have been conducted in Western and Asian countries, particularly focusing on COPD and lung cancer.[13] There is limited research on this topic within Pakistan. Studies conducted in Pakistan have primarily focused on other aspects of lung diseases, such as the epidemiology of ILDs and the use of neuropeptides in asthma and COPD treatment.[14] However, the role of the microbiome in these diseases has not been thoroughly explored in local settings.

International studies have consistently highlighted the impact of microbiome dysbiosis on the severity and prognosis of lung diseases. For example, Lira-Lucio et al. (2020) emphasized the role of the lung microbiome in modulating immune responses in diseases like asthma and COPD.[15] Similarly, Meng et al. (2023) reviewed the relationship between lung microbiota and lung

cancer, suggesting that microbial imbalances contribute to tumorigenesis and therapeutic resistance.[13] Our findings align with these studies, showing that microbiome alterations are more pronounced in severe disease cases, particularly in lung cancer and COPD. Furthermore, the correlation between smoking history and microbiome dysbiosis observed in this study is consistent with global findings, where smoking is known to significantly affect microbial diversity.[16]

In Pakistan, studies such as Jafri et al. (2020) and Shakoor et al. (2023) have documented the prevalence and clinical features of ILDs, but the role of the microbiome in these diseases remains largely unexplored.[14,3] Our study fills this gap by providing novel data on microbiome dynamics in ILD patients, offering new perspectives for future research.

In contrast to the substantial body of research from the United States and Europe, which have focused extensively on the microbiome's role in COPD exacerbations and lung cancer.[13] Studies in Pakistan have generally not explored these microbiome-disease interactions. The study by Whiteside et al. (2021) on the dynamic nature of the lung microbiome in COPD exacerbations highlights the importance of understanding how microbial shifts influence disease severity and treatment outcomes.[17] Our findings, showing a significant association between dysbiosis and poor treatment response, support these findings. Moreover, studies in countries like China and Korea have shown that microbiome imbalances are associated with COPD and asthma.[16] Further confirming the global relevance of our findings.

The results of this study contribute to the growing body of literature on lung microbiome research, providing valuable insights into the role of microbiota in lung disease pathogenesis. The identification of specific microbial signatures associated with different lung diseases opens avenues for potential diagnostic biomarkers and personalized treatment strategies. Moreover, the findings that microbiome dysbiosis correlates with treatment resistance suggest that microbiome modulation could be a promising therapeutic approach. This aligns with studies by Fabbrizzi et al. (2019), which explored the therapeutic potential of probiotics in restoring microbial balance and improving disease outcomes.[9]

Study Limitations and Future Directions: While this study provides valuable insights, it is not without limitations. The retrospective nature of the study means that it relies on pre-existing medical records, which may have incomplete or inconsistent data. Additionally, the cross-sectional design does not allow for a temporal analysis of microbiome changes over time. Future studies with longitudinal designs, incorporating direct microbiome sampling and sequencing, will provide a more comprehensive understanding of the dynamics of the lung microbiome in pulmonary diseases. Furthermore, incorporating a broader range of biomarkers and using advanced genomic techniques could further elucidate the mechanisms by which the microbiome influences disease progression and response to treatment.

In conclusion, this study highlights the significant role of the lung microbiome in pulmonary diseases, particularly in the context of COPD, asthma, lung cancer, and ILDs. By integrating microbiome analysis with clinical data, this research provides a foundation for future studies aiming to explore microbiome-based interventions for the treatment of lung diseases.

CONCLUSION

This study highlights the significant role of the lung microbiome in pulmonary diseases such as COPD, asthma, lung cancer, and ILDs. The results reveal that microbiome dysbiosis is prevalent across these conditions, particularly in lung cancer, and is associated with poor treatment outcomes. Age, smoking history, and disease severity were found to influence the composition of the lung microbiome, suggesting that microbial imbalances may contribute to disease progression and therapeutic resistance. The findings underscore the potential of microbiome-based interventions as a promising therapeutic avenue for improving lung disease management.

Future research should focus on longitudinal studies with direct microbiome sampling to better understand the temporal dynamics of microbiome alterations in pulmonary diseases. Additionally, exploring microbiome modulation as a therapeutic strategy could provide valuable insights into personalized treatments for patients with lung diseases.

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