ORIGINAL RESEARCH

Global Research Trends on the Link Between the Microbiome and COPD: A Bibliometric Analysis

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Background: The pathogenesis of chronic obstructive pulmonary disease (COPD) has been studied in relation to the microbiome, providing space for more targeted interventions and new treatments. Numerous papers on the COPD microbiome have been reported in the last 10 years, yet few publications have used bibliometric methods to evaluate this area.

Methods: We searched the Web of Science Core Collection for all original research articles in the field of COPD microbiome from January 2011 to August 2022 and used CiteSpace for visual analysis.

Results: A total of 505 relevant publications were obtained, and the number of global publications in this field is steadily increasing every year, with China and the USA occupying the first two spots in international publications. Imperial College London and the University of Leicester produced the most publications. Brightling C from the UK was the most prolific writer, while Huang Y and Sze M from the USA were first and second among the authors cited. The *American Journal of Respiratory and Critical Care Medicine* had the highest frequency of citations. The top 10 institutions, cited authors and journals are mostly from the UK and the US. In the ranking of citations, the first article was a paper published by Sze M on changes in the lung tissue's microbiota in COPD patients. The keywords "exacerbation", "gut microbiota", "lung microbiome", "airway microbiome", "bacterial colonization", and "inflammation" were identified as cutting-edge research projects for 2011–2022.

Conclusion: Based on the visualization results, in the future, we can use the gut–lung axis as the starting point to explore the immunoinflammatory mechanism of COPD, and study how to predict the effects of different treatments of COPD by identifying the microbiota, and how to achieve the optimal enrichment of beneficial bacteria and the optimal consumption of harmful bacteria to improve COPD.

Keywords: COPD, microbiome, bibliometric analysis, CiteSpace, gut microbiome, respiratory microbiome, bacterial colonization

Introduction

Chronic obstructive pulmonary disease (COPD), a respiratory condition marked by recurrent respiratory problems and air trapping brought on by abnormalities in the airways and/or alveoli, is frequently linked to prolonged exposure to harmful particles, with chronic cough, expectoration, shortness of breath, or dyspnea as the main symptoms, with high prevalence and case fatality.[1–4] In 2020, it became the third-ranking cause of death globally.[5–7] Especially in the world of novel coronavirus pneumonia, COPD sufferers are more prone to cause serious illness and death,[8] so in the situation of the global spread of the epidemic, the diagnosis and treatment of COPD patients is particularly important.

A group of microbes that reside on and in the human body is known as the human microbiome[9] and interact with the environment, enabling special metabolic processes for the human host as well as microbial environmental stimuli.[10] Studies had shown that the microbiota was vital to the onset, development, and progression of lung illness.[8,11,12] *Lachnospiriaceae* was favorably connected with COPD severity, while *Parabolides goldsteinii* and *Escherichia coli* were negatively correlated.[13] Additionally, an imbalance in the lung microbiota can worsen COPD by downregulating miR-122 and miR-30a and enhancing the expression of interleukin-17a (IL-17a).[14] An alternate method to treat COPD is to consume bad bacteria as much as possible or to enrich helpful bacteria as much as possible, for example, the isolated strains of *Parabacteroides goldsteinii MTS01*, *Bifidobacterium brew* and *Lactobacillus rhamnosus* can reduce

inflammation of the airways and alveoli injury in COPD mice.[13,15] A growing body of evidence[13–17] also revealed that COPD patients had a different microbiome than healthy people and that the associated beneficial microorganisms, pathogenic organisms, and their induced immune flammatory responses were helpful to explore its pathogenesis, allowing space for more targeted interventions and new treatments. Numerous papers in the area of the microbiome in COPD had been published during the previous 10 or so years to characterize this dynamic interaction between microorganisms, therapeutics, and disease states. The massive literature growth necessitates new methods for reviewing and trend analysis. However, to date, no bibliometric research on microbiome in COPD have been reported.

The statistical evaluation and quantification of academic publications is known as bibliometrics[18] and has been applied in many research areas to evaluate countries, organizations, authors, journals, cited references, and pertinent keywords.[19] One of the most often used bibliometric analysis programs is CiteSpace, which was invented in early 2004 by Professor Chaomei Chen to explore the dynamic evolution of the development of the discipline.[20–22] According to the bibliometric program CiteSpace, this study systematically analyzed the overall trend of the microbiota of COPD patients in the past decade through the time mapping from research frontiers to knowledge bases, using the most commonly used database in econometric research,[23] namely Web of Science Core Collection (WoSCC), also foresaw potential new academic frontiers and spots in the future. This is wished here that work will offer some reference value for researchers in the field and encourage further development in this area.

Methods

Information Sources and Search Tactics

The WOSCC database was selected as the goal resource for the primary article search. WOSCC serves as the most popular and reliable web browser for academic literature, offering thorough coverage of important scientific outcomes across the globe.[24] Numerous research have made extensive use of relevant research assessment and visualization of scientific literature.[25–28] To guarantee the completeness of the bibliographic data, the search index utilized by WoSCC was standardized to cover all pertinent articles.

The following terms were included in the search method for both COPD and microbiota: TS= (microbiota OR microbial community OR microbial community composition OR microbial community structure OR human microbiome OR microbiome) AND TS= (chronic obstructive lung disease OR chronic obstructive pulmonary disease OR COAD OR COPD OR chronic obstructive airway disease OR chronic airflow obstruction) and the search dates are from 1 January 2011, to 31 August 2022. The extraction and output of documents should be completed within a day to eliminate bias brought on by continuing database updates (September 14, 2022). The National Library of Medicine (NLM)/PubMed provided a list of Medical Subject Headings (MeSHs), from which the aforementioned keywords were selected.

Inclusion and Exclusion Criteria

The following were the study's inclusion and exclusion criteria: (1) The time period covered 13 years from 2010 to 2022; (2) only reviews and articles were included, and additional documentation categories (such as book chapters, proceedings papers, letters, publications that have been retracted, and editorial materials) were removed; (3) duplicate publications were excluded; (4) unpublished articles were excluded; and (5) irrelevant articles were excluded.

Data Analysis and Visualization

For visual analysis, the ultimate selected publications were loaded into CiteSpace (6.1.R3) and Microsoft Excel. The amount of papers produced each year was trended using Microsoft Office Excel. CiteSpace is a data analysis and document visualization application. Dr Chaomei Chen of Drexel University in Philadelphia, Pennsylvania, developed it. Co-occurring keyword, Co-authors and Co-citations analyses are just a few of CiteSpace's outstanding features. It aids in offering clear instructions for moving on with analysis in a particular area of research.[29] The following CiteSpace settings are in place: time slicing (from 2010 to 2022, years per slice = 1), node type (Select one option from keywords, countries, institutions, authors, references, cited authors and cited journals each time), links (scope: within slices, strength: cosine),

selection criteria (g-index: k = 25). When the node is a keyword, the clipping method is selected Pruning the merged network, Pruning sliced networks, pathfinder.

Results

Article Distribution by Years of Publication

Considering the inclusion and exclusion criteria, a total of 505 articles were finally obtained after deleting 128 non-conforming records. The annual amount of papers pertaining to the COPD microbiome increased steadily, according to the worldwide trend in publication numbers shown in Figure 1. The quantity of books published in 2021 was the highest over the past decade,[30] and since 2018, the number of publications has been greater than 50 each year. It is possible to estimate that the number of books published will keep growing gradually inside the years to come based on the expansion curve of articles over time.

In terms of the three highest prolific nations' annual publications, the US consistently maintains high levels of output. China has seen the fastest growth, with annual production surging since 2018, surpassing the USA to peak in 2021. The UK's trend in the volume of publications has also shown an overall growth trend in the last 10 years, reaching a peak in 2020. These findings suggest that study on the microbiota and COPD is expanding internationally.

Analysis of Countries or Regions

The papers on the study of the COPD microbiome included contributions from 49 nations or regions. Table 1 lists the best 10 nations or regions based on publications and centrality. The leading five countries in counts of papers were the USA, China, the UK, Australia, and Spain, whereas the top five nations in regards to centrality were the UK, the USA, Australia, Denmark, and Spain. China came in second with 111 papers, trailing the USA's 144 papers as the more prolific nation. In Northern America and Europe, the USA, the UK, and Spain had the highest rates of productivity. In Oceania and Asia, China and Australia had the highest rates of productivity. The USA came in second with a centrality of 0.23, trailing only the UK with a 0.31 score, and Australia had the third centrality at 0.17. The UK, the USA, Australia, and Denmark all have a centrality of larger than 0.1, suggesting that those same four nations have some bearing on the research of the microbiome in COPD. High-productivity countries rank high level of publications and centrality, demonstrating that their influence on the world was inversely correlated with their output.
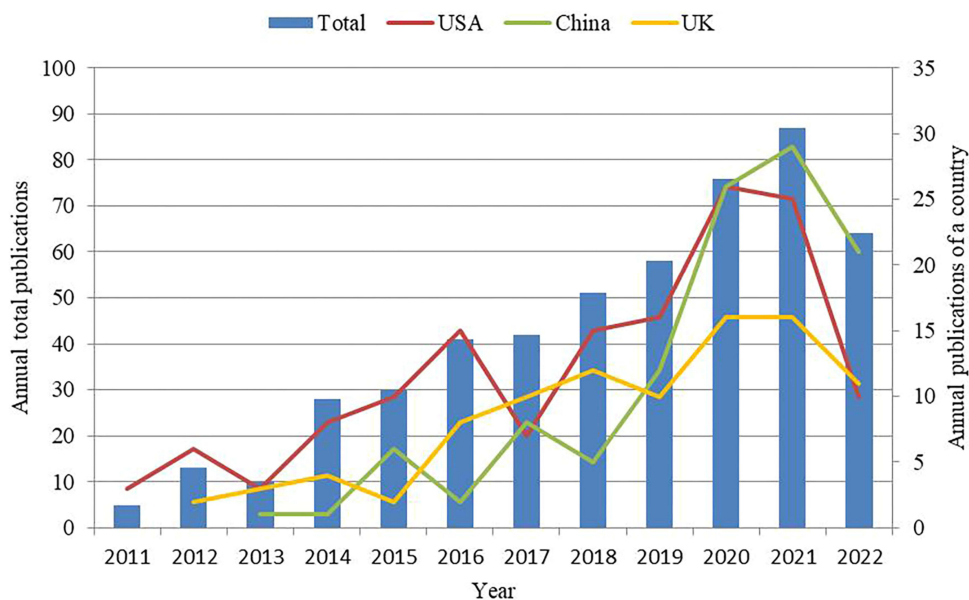

Figure 1 The quantity of yearly publications.

Table 1 The Top 10 Countries or Regions in Aspects of Articles Published and Importance

Rank	Publications (% of 505)	Country	Rank	Centrality	Country
1	144 (28.5)	USA	1	0.31	UK
2	111 (22)	China	2	0.23	USA
3	94 (18.6)	UK	3	0.17	Australia
4	46 (9.1)	Australia	4	0.13	Denmark
5	37 (7.3)	Spain	5	0.09	Spain
6	37 (7.3)	Italy	6	0.09	Canada
7	26 (5.1)	Canada	7	0.08	Italy
8	24 (4.7)	France	8	0.08	France
9	24 (4.7)	Germany	9	0.08	Netherlands
10	22 (4.3)	Netherlands	10	0.08	Switzerland

Figure 2 displays the cooperation network diagram between nations/regions. There are 49 nodes and 187 lines in this network, and its density is 0.159. Nodes in the map represent countries. The yearly circle width shows how many articles the nation publishes in a specific year. The annual ring gets broader the more publications that year are published. Cooperation relations are represented by lines connecting the nodes. The wider the line, the stronger the relationships. Overall, the top 10 countries or regions, as determined by publications and centrality, collaborate with one another, with the USA and the UK in particular having the largest number of national collaborators.

Analysis of Institutions

From 2011 to 2022, 321 institutions in total listed inside this area. The 10 leading institutions, as determined by publications and centrality, are shown in Table 2. Imperial College London, University of Leicester, University of Manchester, University of Queensland, and Newcastle University were the list of top institutions. The five most important institutions in aspects of centrality were University of Michigan (0.19), Imperial College London (0.16), University of Dundee (0.13), University of Leicester (0.10) and University of Southampton (0.08). The centrality of University of Michigan, Imperial College London, University of Dundee and University of Leicester is greater than 0.1, showing that they have some impact inside the research on the microbiome and COPD. Institutions have mostly been centered at universities as well as a small number of hospitals, and were mainly located in the UK.
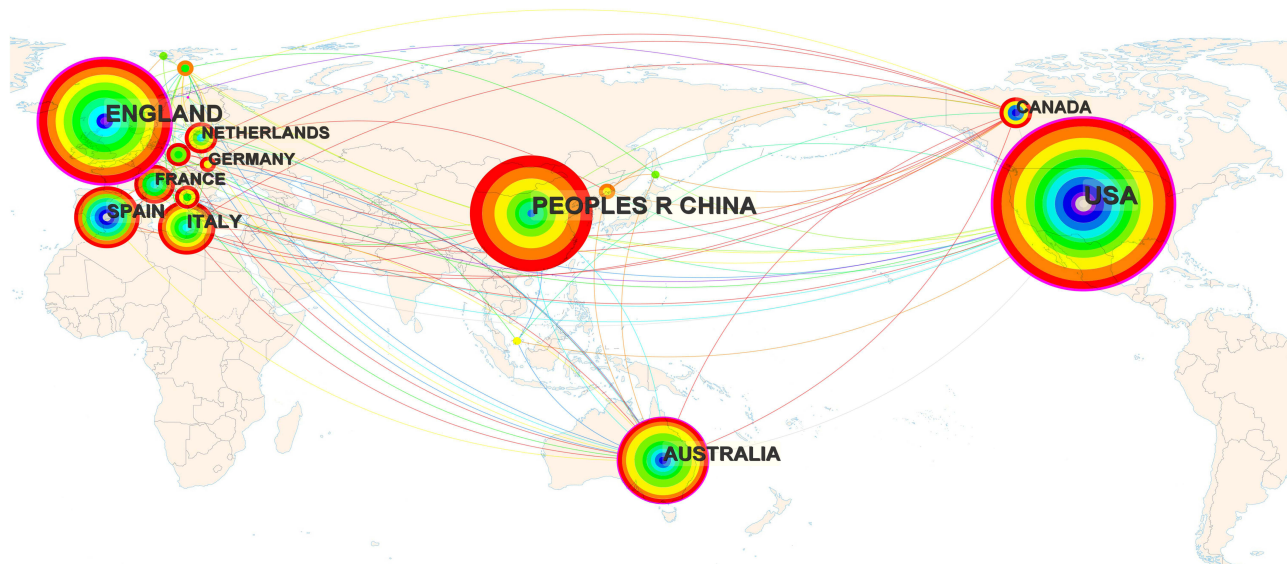

Figure 2 Visualization map of countries or regions.

Table 2 Top ten10 Institutions in Respect of Centrality and Amount of Publications

Rank	Publications (% of 505)	Institution	Country	Rank	Centrality	Institution	Country
1	19 (3.8)	Imperial College London	UK	1	0.19	University of Michigan	USA
2	18 (3.5)	University of Leicester	UK	2	0.16	Imperial College London	UK
3	16 (3.2)	University of Manchester	UK	3	0.13	University of Dundee	UK
4	15 (2.9)	University of Queensland	Australia	4	0.10	University of Leicester	UK
5	14 (2.8)	Newcastle University	UK	5	0.08	University of Southampton	UK
6	12 (2.4)	Guangzhou Medical University	China	6	0.08	AstraZeneca	UK
7	11 (2.2)	University of Southampton	UK	7	0.08	University of Valencia	Spain
8	10 (2.0)	Prince Charles Hospital	Australia	8	0.07	British Columbia Cancer Agency	Canada
9	10 (2.0)	AstraZeneca	UK	9	0.06	University of Manchester	UK
10	9 (1.8)	University of Michigan	USA	10	0.06	Autonomous University of Barcelona	Spain

Extensive cooperation between institutions were discovered as a result of the created institutional mesh node, which showed 321 nodes and 691 link lines representing the institutions with their collaborative links, accordingly (Figure 3A). Imperial College London, for example, which was symbolized by the greatest node, exhibited the most care coordination including several universities, such as University of Leicester, University of Queensland, Newcastle University, University of Manchester, Southern Medical University, University of Technology Sydney.

Examination of Authors and Those Cited

To find possible relationships, the co-authorship and writers who were mentioned were examined. With 378 nodes and 1008 links, the co-authorship network (Figure 3B) was constructed. As a result of his outstanding impact on the development of this subject, Brightling C from the UK held the top spot with all writers in the study of the microbiota
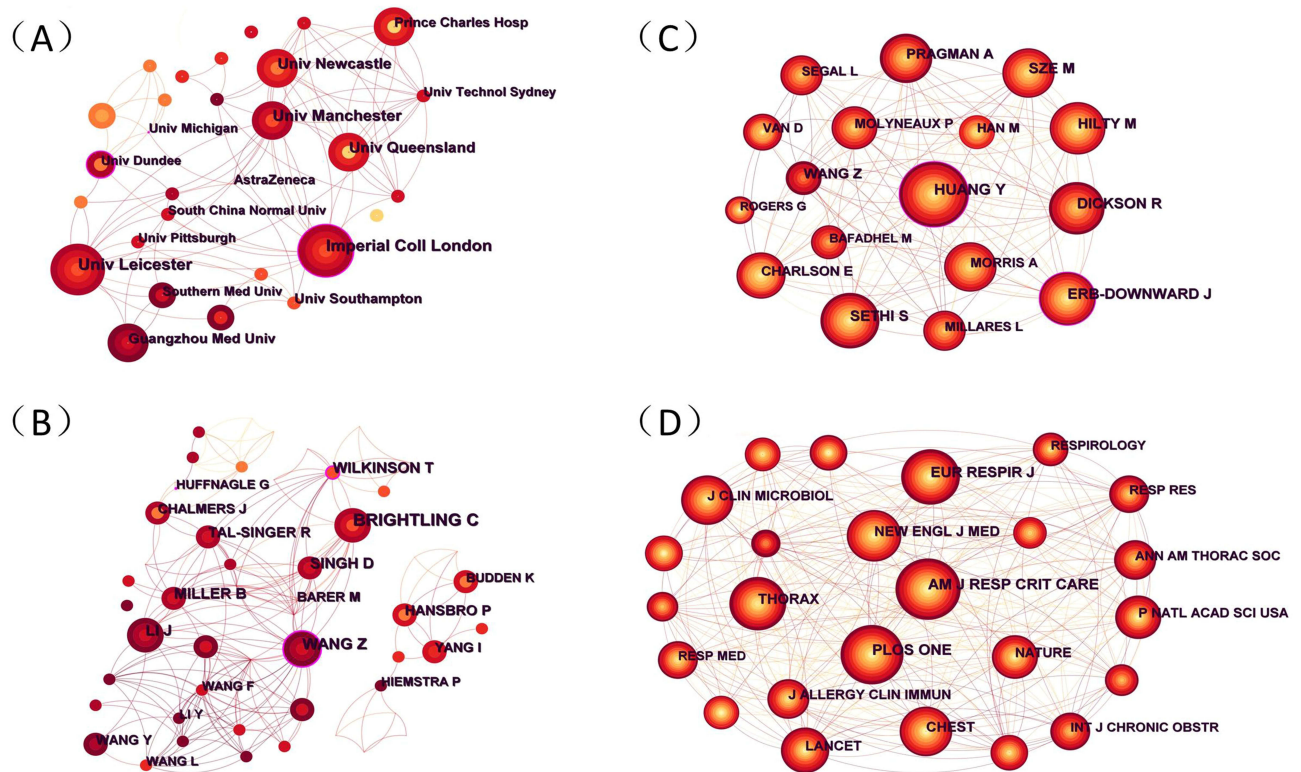

Figure 3 (**A**) A visualization map of institutions. (**B**) A visualization map of authors. (**C**) A visualization map of cited authors. (**D**) A visualization map of cited journals.

Table 3 Top 10 Authors, Include Highly Cited and Prolific Writers

Rank	Publications	Centrality	Author	Country	Rank	Citation Counts	Centrality	Cited Author	Country
1	18	0.08	Brightling C	UK	1	151	0.11	Huang Y	USA
2	14	0.11	Wang Z	USA	2	130	0.04	Sze M	USA
3	12	0.02	Singh D	UK	3	127	0.05	Sethi S	USA
4	11	0.04	Li J	UK	4	125	0.04	Dickson R	USA
5	11	0.10	Miller B	USA	5	124	0.10	Erb-Downward J	USA
6	11	0.12	Wilkinson T	UK	6	117	0.06	Hilty M	Switzerland
7	10	0.03	Hansbro P	Australia	7	103	0.05	Pragman A	USA
8	10	0.06	Tal-Singer R	USA	8	92	0.01	Wang Z	USA
9	9	0	Barer M	UK	9	88	0.07	Charlson E	USA
10	9	0.09	Chalmers J	UK	10	78	0.03	Morris A	USA

in COPD. The two next-most prolific writers are Wang Z from the USA and Singh D from the UK, with 14 and 12 publications, respectively. We discovered that writers who produced a significant amount of publications typically had set partners and, as a result, formed their own research groups. In accordance with the findings of the 10 largest productive countries, the majority of the leading 10 authors originate from the UK, with a small number coming from the USA and Australia (Table 3).

Figure 3C displays the network of cited authors, with 559 nodes and 3166 links. In total, 559 authors were cited, of which 7 were referenced at over 100 times. The American researcher Huang Y had the most citations (n = 151), following after Sze M (n = 130), and Sethi S (n = 176). Nine of the top 10 most mentioned writers are all Americans (Table 3).

Analysis of Cited Journals

To identify the interconnectedness and cross-relationship across journals in the study of the COPD microbiome, analysis of referenced journals was done. Table 4 contains information about the top 10 referenced journals in this field, and Figure 3D shows a map of the pertinent body of knowledge. The *American Journal of Respiratory and Critical Care Medicine* (341 citations), *PLoS One* (338 citations), *European Respiratory Journal* (291 citations), *Thorax* (273) and *The New England Journal of Medicine* were the top five cited journals (240). Among top 10 most referenced journals, *Lancet* had an IF of 202.73, which was followed by *The New England Journal of Medicine*, which had an IF of 176.079. The foundation of this discipline is shown in the published citations of such prestigious journals. The lion's share of the top 10 journals are high-caliber American and British periodicals.

Table 4 Top 10 Cited Journals

| Rank	Journal	Frequency	JCR	IF	Country
1	*American Journal of Respiratory and Critical Care Medicine*	341	Q1	30.528	USA
2	*PLoS One*	338	Q2	3.752	USA
3	*European Respiratory Journal*	291	Q1	33.795	UK
4	*Thorax*	273	Q1	9.102	UK
5	*The New England Journal of Medicine*	240	Q1	176.079	USA
6	*Chest*	220	Q1	10.262	USA
7	*Lancet*	196	Q1	202.731	UK
8	*Journal of Clinical Microbiology*	176	Q1	11.677	USA
9	*Proceedings of the National Academy of Sciences of the United States of America*	169	Q1	12.779	USA
10	*Journal of Allergy and Clinical Immunology*	167	Q1	14.290	USA
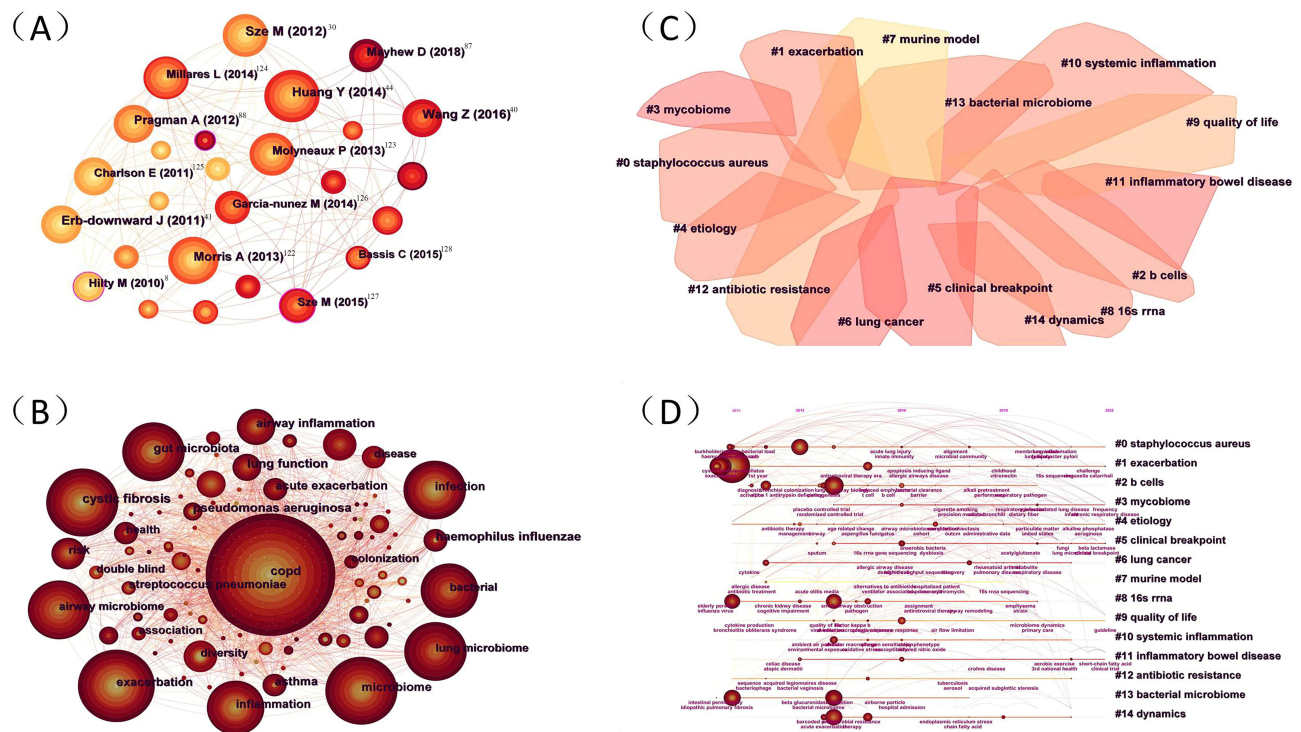
Figure 4 (**A**) Visualization map of cited references. (**B**) Co-occurring keywords map. (**C**) The cluster of keywords. (**D**) Timeline view for keywords.

Analysis of Cited Reference

The condition of cited literature in this area is shown in Figure 4A, which featured a network with 581 nodes and 2549 links. The 10 leading publications in terms of number of references are detailed in Table 5, with the most popular article, "The lung tissue microbiome in chronic obstructive pulmonary disease", written by Sze et al and posted in the *American Journal of Respiratory and Critical Care Medicine* in 2012, receiving the highest number of citations.[31] Among the 10 leading documents, 4 were published in the *American Journal of Respiratory and Critical Care Medicine*, two in the *PLoS One*, respectively, while the rest of the group were authored in different journals. These 10 references could be considered as the most popular articles and fundamental research inside this ground.

Analysis of Keywords and Research Hotspots

Hot subjects are represented by keywords with a high frequency, while terms with a significant centrality show the impact of relevant research in a particular area. The keyword co-occurrence knowledge map (Figure 4B) contained 381 nodes and 718 lines. Table 6 lists the most popular 10 high-frequency keywords here on subject, which were COPD, exacerbation, gut microbiota, microbiome, cystic fibrosis, lung microbiome, infection, bacterial, airway microbiome and inflammation. The most crucial 10 keywords were bacterial colonization, COPD, *pseudomonas aeruginosa*, diversity, 16s ribosomal rna, cystic fibrosis, association, inflammatory bowel disease, T cell and asthma. In addition, keyword clustering visualization was also constructed, as shown in Figure 4C. In the study of the microbiome in COPD, there have been 15 clustering patterns. The specifics are displayed in Table 7.

The microbiome research in the field of COPD mainly focused on gut microbiota and respiratory microbiome, and 16s RNA technology was often used for detection. Inflammation was important in the etiology of COPD, as well as the combination of inflammatory bowel illness could increase the mortality risk in COPD patients.[40] The pathogenesis of the disease also included infection, bacteria, T cell immunity, B cell immunity, etc. Patients with COPD frequently have *Staphylococcus aureus* and *Pseudomonas aeruginosa* in their bodies. The top keyword in terms of centrality was bacterial colonization, and this was one of the primary factors in the severe COPD exacerbation.[41]

Table 5 Top 10 Cited References

Rank	Title	Cited Frequency	First Author	Year	Journal	JCR	IF
1	The lung tissue microbiome in chronic obstructive pulmonary disease[31]	59	Sze M	2012	*American Journal of Respiratory and Critical Care Medicine*	Q1	30.528
2	Lung microbiome dynamics in COPD exacerbations[32]	56	Wang Z	2016	*European Respiratory Journal*	Q1	33.795
3	Analysis of the Lung microbiome in the "healthy" smoker and in COPD[33]	54	Erb-downward J	2011	*PLos One*	Q2	3.752
4	Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease[34]	54	Huang Y	2014	*Journal of Clinical Microbiology*	Q1	11.677
5	Comparison of the respiratory microbiome in healthy nonsmokers and smokers[35]	46	Morris A	2013	*American Journal of Respiratory and Critical Care Medicine*	Q1	30.528
6	The lung microbiome in moderate and severe chronic obstructive pulmonary disease[36]	45	Pragman A	2012	*PLoS One*	Q2	3.752
7	Longitudinal profiling of the lung microbiome in the AERIS study demonstrates repeatability of bacterial and eosinophilic COPD exacerbations[30]	44	Mayhew D	2018	*Thorax*	Q1	9.102
8	Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease[37]	43	Molyneaux P	2013	*American Journal of Respiratory and Critical Care Medicine*	Q1	30.528
9	Bronchial microbiome of severe COPD patients colonised by *Pseudomonas aeruginosa*[38]	38	Millares L	2014	*European Journal of Clinical Microbiology*	Q3	5.103
10	Topographical continuity of bacterial populations in the healthy human respiratory tract[39]	37	Charlson E	2011	*American Journal of Respiratory and Critical Care Medicine*	Q1	30.528

Table 6 The 10 Most Popular Keywords in Regards to Frequency and Centrality

Rank	Frequency	Keywords	Rank	Centrality	Keywords
1	293	COPD	1	0.31	Bacterial colonization
2	100	Exacerbation	2	0.21	COPD
3	83	Gut microbiota	3	0.21	*Pseudomonas aeruginosa*
4	77	Microbiome	4	0.2	Diversity
5	74	Cystic fibrosis	5	0.17	16s ribosomal rna
6	72	Lung microbiome	6	0.16	Cystic fibrosis
7	68	Infection	7	0.16	Association
8	67	Bacterial	8	0.16	Inflammatory bowel disease
9	66	Airway microbiome	9	0.14	T cell
10	60	Inflammation	10	0.12	Asthma

Table 7 Clustering of Keywords of COPD Microbiome-Related Research

Cluster	Size	Silhouette	Mean(Year)	Label (LLR)
0	37	0.867	2016	*Staphylococcus aureus*
1	34	0.889	2015	Exacerbation
2	29	0.892	2015	B cells
3	28	0.891	2018	Mycobiome
4	28	0.788	2017	Etiology
5	26	0.858	2019	Clinical breakpoint
6	26	0.853	2018	Lung cancer
7	25	0.935	2015	Murine model
8	24	0.863	2015	16s rRNA
9	24	0.799	2015	Quality of life
10	23	0.969	2016	Systemic inflammation
11	22	0.929	2017	Inflammatory bowel disease
12	18	0.98	2015	Antibiotic resistance
13	16	0.978	2013	Bacterial microbiome
14	15	0.92	2016	Dynamics

In addition, the emergence and progress of frontier research themes can be reflected in the timeline view of keywords (Figure 4D) and keyword burst term map (Figure 5). We found that "staphylococcus aureus" (Cluster 0), "exacerbation" (Cluster1), "B cells" (Cluster2), "etiology" (Cluster 4), "lung cancer" (Cluster 6), "16s rRNA" (Cluster 8), "quality of

Top 8 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2011 – 2022
bacterial colonization	2011	4.73	2011	2016	
community-acquired pneumonia	2011	2.94	2011	2014	
diversity	2011	2.64	2011	2014	
sputum	2011	3.08	2014	2016	
chronic bronchiti	2011	3.02	2014	2016	
bacterial microbiome	2011	3.02	2014	2016	
community	2011	3.53	2015	2019	
nontypable haemophilus influenzae	2011	2.59	2016	2018	

Figure 5 Top eight keywords with the strongest citation bursts.

life" (Cluster 9), "antibiotic resistance" (Cluster 12) and "bacterial microbiome" (Cluster 13) were a relatively early hotspot, and "mycobiome" (Cluster 3), "clinical breakpoint" (Cluster 5), "murine model" (Cluster 7), "systemic inflammation" (Cluster 10), "inflammatory bowel disease" (Cluster 11) and "dynamics" (Cluster 14) were hot spots in the middle and late stages. Furthermore, *Staphylococcus aureus*, exacerbation, mycobiome, etiology, clinical breakpoint, quality of life, inflammatory bowel disease have continued on the timeline, which may be the focus of research in the next few years. The keyword "bacterial colonization" appeared in 2011 is the most explosive keyword, followed by "community" and "sputum". In contrast, "community" and "non-typable haemophilus influenzae" were the terms that appeared more frequently in the last 5 years.

Discussion
General Trends
In this work, CiteSpace was employed to conduct a thorough evaluation of ongoing research on the connection between COPD and the microbiota, identify hot themes in this field, and forecast prospective future directions for research. From 2011 to 2022, 505 papers about the microbiota and COPD were found by searching the WOSCC. In respect of yearly articles, we discovered that this field's publications increased gradually annually, particularly after 2020, which demonstrates that scholars from all nations continued to pay attention to and show interest in this topic. This represented the recognition of the majority of scholars on the results of recent study in this area and the continuous research on the unknown and problems worth further exploration in this field. For example, more and more evidence showed that probiotics (*Bifidobacterium*,[42] *Lactobacillus plantarum*,[43] etc) can protect and treat lung diseases by optimizing the balance of gastrointestinal microorganisms (stimulating the balance of Th1/Th2,[42] lowering the lung's innate immune cell count,[43] etc), but its therapeutic effect on COPD, exact mechanism, and many aspects of regulating immune response are still largely unknown.[15] These unknowns can stimulate the motivation of researchers, and lay a good foundation for further exploring the internal relationship between COPD and microbiome, searching for its potential mechanisms, and developing potential beneficial bacteria strains and their functional components to treat COPD.

Analysis of Contributions from Nations/Regions, Organizations, and Journals
An assessment of annual papers related to the COPD microbiome found that the USA and the UK were the highest ranked nations in regards to central location, publishing more than 47% of the 505 publications, according to a visual analysis of the dispersion of countries, which showed that they were not only the most active countries that publish papers but also had great influence. In terms of research institutions, Imperial College London (UK) was the most productive research institution, and the research university with the greatest centrality was the University of Michigan (US), and the proportion of the USA and the UK in the 10 leading nations for productivity and centrality was more than half, which showed that the two countries' prominence in this field of study. This may be related to the fact that both the University of Michigan and Imperial College London have top national lung research institutes, which have trained a large number of high-quality talents. For example, from Imperial College of Technology, Peter J Barnes, was one of the core expert group members of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. He has written more than a thousand peer-reviewed articles in asthma, COPD, other relevant fields (h-index 186, cited more than 150,000 times), which has a huge impact. To sum up, the study of the link with COPD and microbiota is primarily conducted in the USA and the UK.

The number of papers published by China ranked second, demonstrating China's substantial influence in this area. It was worth noting that in Table 2, except for China, other research institutions were located in industrialized nations, particularly the UK, the USA and Australia. This demonstrated that national impact on the world stage was inversely correlated with research institution production, and they showed great academic influence in this field. At the same time, Figures 2 and 3A show the tight collaboration between many nations and institutions, including close cooperation between China and European and American countries. In the context of global cooperation commons, researchers from many countries will cooperate to conduct more and more important research in the future, which will encourage the growth and consolidation of this field's knowledge.

The 10 most popular journals, which were those that had produced high-quality studies and aroused the interest of researchers engaged in this area, are listed in Table 4. The findings of our study will aid researchers in this area in quickly locating pertinent publications, obtaining the most recent developments in COPD microbiology research, or submitting their works.

Influential Authors and Studies

Brightling C from the University of Leicester in the UK was the writer who had the most articles. His research has long focused on asthma, immunology, internal medicine, COPD and problems in sputum, and combined the topics of microbiome, lung disease, deterioration, lung and biomarkers with his research on COPD. In 2021, in a study his team conducted comparing the pulmonary microbiomes of healthy people and COPD patients, they found that as the disease got worse, the microbiomes of the lungs changed, the airway microbiome is connected to the decreased abundance of *Prevotella* and increased abundance of *Moraxella*.[44] In another study, his team discovered that in some cases, eosinophilic and neutrophilic COPD are convertible, and that by tracking the respiratory microbiome's temporal variability, one may follow the inflammation condition of patients across time.[45] His and his team's research has laid a good foundation for future scholars to explore the host microorganism interaction of COPD and the related immune response of lung microorganisms in COPD. Additionally, we discovered that University of Michigan student Yvonne J. Huang received the most citations. She is mainly engaged in the study of the microbiome–host interactions in COPD pathogenesis and phenotypes. For example, according to one of her studies, changes in the heterogeneity of the bronchial microbiome were associated with the progression of COPD, an upsurge in the species that are home to common COPD pathogens, and a decrease in the number of microbiota members that provide assistance to the structure and functionality of homeostasis.[46] In terms of the quantity of published papers and publications referenced, Zhang Wang from the School of Life Sciences at South China Normal University ranked the highest 10. He is engaged in the research of respiratory system disease microbiology, and deeply revealed the characteristics of airway microecology in patients with COPD. His study, which was published in Nature Microbiology in 2022, showed that interleukin-22-mediated macrophage-epithelial cell cross-talk prevents lung function decrease, emphysema, apoptosis and neutrophilic inflammation in response to respiratory microbiome-derived IAA.[47] These authors have had a significant academic impact on this field and have made remarkable contributions to its advancement.

The article by Sze[31] that appeared in the *American Journal of Respiratory and Critical Care Medicine* in 2012 is the one that has received the most citations. This study found that the bacterial community in human lung tissue was both observable and dynamic. The follow-up research is mainly based on this to explore what this detectable and changeable bacterial community is, and what is the internal relationship with COPD disease.[45,48,49] Zhang Wang was the author of the second-most-cited paper (*European Respiratory Journal*).[32] This article showed that the change of pulmonary microbiota seemed to be related to the deterioration event, while *Haemophilus* might greatly affect the entire microbial community structure. The third most cited was written by John R Erb Downward (*PLoS One*).[33] The pulmonary microbiome has been further demonstrated in this study, which also highlights macro- and micro-anatomical abnormalities in these microbial flora in individuals who have severe COPD. Based on the correlation between pulmonary microorganisms and COPD deterioration, the follow-up research deeply explored the specific flora and its mechanism leading to the deterioration, and looked for the optimal consumption of potentially harmful bacteria in order to determine potential therapeutic interventions.[47,50,51] Analysis of the network of references reveals that the microbiome mainly studied in the top 10 cited references was from lung tissue and respiratory tract. The authors of these papers observed that the pulmonary microbiota would change when people with exacerbations of COPD,[31,32] and the increased microbiota members were mainly *Proteus*.[34] The most frequently cited articles have a good guiding role within the field, laying a foundation for upcoming studies on the influence and mechanism of the interaction between microorganisms and COPD, and providing a research basis for new prevention and treatment of COPD.

Hotspots and Frontiers

The paper's study theme can be summed up using the keywords that reflect the main thesis and essential elements of the literature. We can therefore identify the current study centers in an area, anticipate future trends in research scientifically, and give researchers a place to start their research by looking at the frequency and centrality of keywords in that field. We analyzed the popular keywords involved in keyword co-occurrence, clustering, timeline and citation bursts, summarizing

the following three major research directions: First, bacterial colonization, mainly involving *Pseudomonas aeruginosa, Haemophilus influenzae* and *Staphylococcus aureus*, is highly close to the deterioration of COPD; the second is respiratory microbiota; the third is gut microbiome: it mainly involves T cells and B cells, and the main representative product is short-chain fatty acid. COPD and inflammatory bowel illness are related. Because inflammation is the pathological basis and core mechanism of COPD, the above three points are mostly combined with inflammation analysis to explore the mechanism of interaction between COPD and microbiome. The following will be elaborated on the basis of these three points, with a view to finding a way forward for researchers.

Bacterial Colonization

The occurrence and development of COPD were related to inflammatory cells, which can produce inflammatory mediators after being activated by stimulators, and then damaged the airway wall and lung tissue.[52,53] When referring to the presence of bacteria on or in the human body, the phrase "colonization" denotes that the host is unaffected by the germs. However, in all stages of COPD, bacterial colonization could enhance airway inflammation in stable COPD, reduce lung function[54–56] and increase systemic inflammatory markers.[57,58] With the decrease of immune capacity of COPD patients in the stable period,[45] lower airway bacterial colonization (LABC) was most likely to occur,[59,60] that is, the lower respiratory tract's mucosal epithelium was covered in a lot of bacterial flora, which absorbed nutrients through the body and grew and reproduce in the lower respiratory tract's mucous epithelium, thus causing host infection.[61] It was proved that there was a clear correlation between bacterial pathogen isolation in peripheral bronchial tree and neutrophil airway inflammation in COPD, and the primary chemokine mediator throughout this mechanism appeared to be IL-8.[62] According to Chung's research,[63] individuals with stable COPD who had bacterial colonization had higher levels of TNF- α, IL-6, and IL-8 in their sputum. Zhang[64] clearly showed how LABC could impact inflammation of the airways and the occurrence of COPD acute exacerbations (AECOPD). If bacterial colonization increased the symptoms of stable COPD, it is expected that treatment (such as preventive antibiotics) can alleviate the COPD patients' clinical signs and symptoms. At present, the species identified from COPD sufferers' lower airways and showing signs of deterioration included[65–67] *Pseudomonas aeruginosa* (PA), *Streptococcus pneumoniae* (SP), *Moraxella catarrhalis* (MC) and *non-typeable Haemophilus influenzae* (NTHI). Other potential pathogens that were not often isolated were *Haemophilus parainfluenzae* and *Staphylococcus aureus*.[60]

Non-Typeable Haemophilus Influenzae

Haemophilus influenzae may be a significant pathogen in both stable COPD and exacerbation of COPD.[68] The bulk of *Haemophilus influenzae* analyzes the evidence in the airways,[69] and the focus of much investigation are NTHI strains. In mice with a cellular and cytokine profile comparable to that of COPD,[47] the retention of NTHI in the lower airway stimulated the respiratory epithelium to release proinflammatory cytokines, particularly those that enhance neutrophil chemokines.[60] The development of small airway illness in COPD patients was aided by NTHI colonization, and the condition of COPD patients' health deteriorated.[70]

Pseudomonas Aeruginosa

PA colonization was a recognized occurrence in COPD patients and hospitalized patients. It was usually seen in the late stage of COPD,[54] which can lead to severe airway inflammation and secondary lung injury, leading to deterioration of clinical conditions.[71] The colonization of PA in COPD was transient or persistent,[72,73] which may be related to *exoU* and *pKL-3* genes.[74,75] PA colonization contributed to the production of autoantibodies against the bacterial/permeability invading protein (BPI), which maked BPI unable to clean pathogenic microorganisms, thus inducing inflammatory reaction.[76] It had also been shown[77] that the mechanism of COPD deterioration was related to the production of IL-6 and IL-8 in bronchial epithelial cells induced by PA-derived flagellin. The meta-analysis also revealed that individuals with COPD had an adjusted higher death risk when PA separated from sputum.[78]

Staphylococcus aureus

Toxins produced by *Staphylococcus aureus* induced necrosis and apoptosis,[79] and triggered cell death via the RIPK1/RIPK3/MLKL cascade reaction, which resulted in the destruction of particular immune cell types, particularly macrophages, thus

leading to inflammatory disorders and impairing bacterial clearance.[80] Violent enterotoxins, such *Staphylococcus aureus enterotoxin B* (SEB), are released as a result of *Staphylococcus aureus* colonization, which has superantigen activity that causes T cells' activation. The research of Wouter Huvenne's team proved that combining SEB with cigarette smoke (CS) exposure led to the production of dense T and B cell aggregates in the lungs, and aggravated the inflammation of mice induced by CS.[81] These results suggest that *Staphylococcus aureus* may have an impact on how COPD develops.

In summary, further elucidation of the pathogenesis of bacterial colonization affecting COPD will perhaps be the subject of current and upcoming studies in this area which could offer new treatment goals for Patients with COPD as well as diagnostic and prognostic indicators.

Respiratory Microbiome

The upper and lower airways (oropharynx, bronchial tree, and lungs) are covered by the respiratory microbiome, which has discrete populations and varying loads,[82,83] which interact with the environment and are influenced by host inflammatory and immune responses, host genetics, and subject disease,[84] presenting pathogenicity or beneficialness. There is mounting evidence that the clinical phenotype, long-term mortality and severity of COPD are all directly related to the respiratory microbiome.[31,85] The diversity and composition of the respiratory microbiome of stable COPD patients varied with age, degree of airflow restriction, frequency of exacerbation, and peripheral blood eosinophils.[86] Dysregulated airway microbiome ecology had been reported to lead to airway inflammation, immune dysregulation, infection susceptibility,[32,87] and alterations in host epithelial repair mechanisms,[44] and its metabolites were also somehow associated with inflammation.[88,89] In slow-onset lung disease, Wang discovered that IAA produced by the respiratory microbiota reduced eosinophil inflammation and epithelial apoptosis.[47] Based on this, a "vicious cycle" hypothesis of chronic inflammation had been proposed, whereby chronic inflammation resulting in the recurring onset of COPD, lowering the lung's immune system's defenses and leading to a dysregulated lung microbiome, which in turn amplified the COPD's continuous inflammatory response and lead to disease progression.[60]

The two main airway inflammatory endotypes in COPD are neutrophilic or eosinophilic inflammation,[49] both mediated through the interaction of microbial metabolism with host gene expression.[47] Wang and his team emphasized the role of the respiratory microbiota in the management of patients based on inflammatory endotypes in COPD.[45] Yadava[90] used lipopoly-saccharide and elastase in mice to induce chronic COPD-like lung inflammation, demonstrating that host microbial crosstalk promotes inflammation. The severity and course of COPD may be functionally influenced by lung microbial dysbiosis,[32,87] and bacterial proteins or metabolites may be used to effectively promote host inflammatory signaling.[30] Airway microbial communities shifted during episodes of healthy and COPD,[36,91] disease exacerbation,[34,92] such as bacteria from the phylum *Mycobacterium, Thicket and Aspergillus*.[44] Whereas members of *Aspergillus, Actinomyces and Thickobacter* were major contributors to palmitate, homocysteine and urate biosynthesis;[93] palmitate activated inflammation-associated enzymes[94] to enhance inflammation;[95] through the ERK1/2 pathway, homocysteine activated the pro-inflammatory substance MMP9;[96] by triggering inflammatory vesicles with the *CCL2* and *NLRP3* genes, urate may potentially cause inflammation;[77] these biosyntheses contributed to the development of COPD inflammation. Over time, the stability of the pulmonary microbiota may decrease in individuals who deteriorate, while recurrent deterioration within subjects was more likely to repeat bacterial and eosinophil deterioration.[30]

Additionally, it has been demonstrated that antibiotic therapy alters the COPD airway microbial population and that treatment with antibiotics alone reduces bacterial abundance, especially in the *Proteobacteria* members.[9] After 8 weeks of daily azithromycin treatment for COPD patients, Segal et al discovered a decrease in respiratory microbial diversity while metabolites produced by the bacteria reduced lung inflammation, indicating that the effect of azithromycin on COPD patients may be partially mediated by interactions between the respiratory microbiome and the host immune system.[89] Also several studies have shown that the airway microbiome abnormalities identified in patients with COPD exacerbations treated with antibiotics are still present 3 months after the exacerbation and may last longer.[34]

In conclusion, as described in the literature, COPD interacts with the pulmonary microbiota based on the idea that persistent inflammation causes disease progression in a "vicious circle". In turn, the ongoing impact of antibiotic therapy on respiratory microbial changes in COPD helps to investigate the feasibility of resident bacteria as potential targets for immunomodulation to identify targets for treatment and intervention.

Gut Microbiome

The lungs and intestines are of the same histological origin, with the epithelial tissues of the lungs and large intestine originating from the proto-intestinal endoderm, and there is synchrony between the lungs and intestines in terms of mucosal immunity. Although COPD is a respiratory disease, it usually occurs in conjunction with chronic gastrointestinal disorders,[97,98] such as inflammatory bowel disease.[99,100] Recent research had connected pulmonary illness development to changes in the composition and function of the gut microbiome,[101–103] discovering that COPD patients' fecal microbiomes and metabolomes differed from those of healthy people.[41] A new idea had been proposed that the "gut–lung" axis mediated the pathogenic link between the microbiota and respiratory diseases.[104] It had been suggested that COPD pathogenesis was associated with imbalance in the gut microbiota,[105] which adversely affected the gut mucosal barrier function and the body's immune response, leading to elevated levels of local and systemic inflammatory mediators, a key mechanism of action in the development of COPD. The pyrin domain-containing protein 3 (NLRP3) has been shown to be a critical bidirectional regulator of the intestinal-pulmonary axis. This stimulated the recruitment of inflammatory cells and altered immunological reaction in the lungs and digestive system, which in turn affected the activity of NLRP3 inflammatory vesicles.[104,106] Furthermore, experimental mice with gut bacteria dysregulation can cause a marked acceleration of neutrophil infiltration by stimulating the action of the organism's TLR4, which in turn induced a large pulmonary response to bacterial attack and thus inflammation.[107] Gut microbes can increase the quantity of extraintestinal T cells, and differentiated T cells with Th1 and/or Th17 pro-inflammatory cell characteristics activated anti-inflammatory or neutrophils cells as extra effector cells to regulate the immune reaction.[108]

In addition to the common mucosal immunity theory, another theory was that the gut flora produced metabolites that influence the immune response in the lungs.[41,109] Li discovered that COPD patients had a different gut flora from healthy people, one that was dominated by *Prevotella* and had reduced amounts of short-chain fatty acids (SCFAs), such as butyrate, propionate and acetate.[110,111] SCFAs played an significant role in vivo[112–115] and were thought to be a group of metabolites that affected inflammation.[116] By interacting with G protein-coupled receptors on cell membranes including HCA2, FFA2, and GRP43, SCFAs can activate downstream effector molecules like NLRP3, PI3K, and MAPK and change helper T cells and dendritic cells.[117,118] SCFAs could also signaled through GPR43 and GPR109A on intestinal epithelial cells to activate NLRP3 inflammatory vesicles causing lung inflammation and immune cell activation.[111] Additionally, the transporter proteins SLC5A8 or SLC16A1 can allow SCFAs to enter cells.[119,120] SCFAs inhibit histone de acetylase (HDAC) activity to regulate the type of immune response.[113] It had been shown that SCFAs played a role in COPD exacerbations, decreased lung function, COPD weight and physical frailty phenotypes, and emotional vulnerability phenotypes, and that it may play a role in controlling a variety of factors connected to the onset and advancement of COPD.[121] Based on these mechanisms, Mao demonstrated that mucosal immunological response in rats with COPD was improved by administering drugs that remodeled the intestinal flora and inhibited the SCFAs/GPR43/NLRP3 pathway.[122] We require a deeper comprehension of these systems in the future to facilitate the generation and development of more effective therapeutic intervention options.

To sum up, there is still a lot of work to be done in the study of COPD and gut microbiome. To define the mechanisms and clarify the link in greater detail, more study is required. How to explore its related mechanisms in depth from the viewpoint of the gastrointestinal-pulmonary axis and integrate the research results with clinical practice to generate more effective therapeutic interventions will be another hot spot for future research.

Strengths and Limitations

While CiteSpace-based analysis allows for more comprehensive and objective data analysis than traditional overviews, the study design has some constraints. First, if only the WoSCC database is searched, papers that are only available in other databases like Scopus and PubMed may not be found, which could lead to biased and incomplete studies that are included. Second, only articles and reviews are included, not book chapters, conference papers, letters, etc, which can lead to omissions. Finally, the publication deadline for our inclusion in our analysis is August 31, 2022, and although this already reflects the current situation and hotspots in the field, the data collected by the WOS core are constantly updated, but some newly published papers may have been overlooked; consequently, our articles do not accurately depict 2022. However, due to the credibility of the WoSCC database and the large number of publications analyzed, we believe that

this study can still be utilized to illustrate current trends and research centers in the area. Future research with comparable objectives may take note of and overcome these constraints.

Conclusion

In summary, this analysis employed CiteSpace bibliometric analysis tools for the initial time to research the microbiome's role in COPD and its hot topics from 2011 to 2022, and provided the latest analysis of relevant scientific outputs in this area. Every year, there are more publications in this field of study. The three countries that produce the most articles in this field of research are the USA, China, and the UK. Close international scientific cooperation, institutional cooperation and cooperation between researchers had been observed in this area, with institutional cooperation concentrated in universities. Due to the diversity of research directions, there was a variety of journals for researchers to choose from. Current research focused on inflammation, bacterial colonization, respiratory microbes, and gut microbes, which may be new research frontiers, and their outbreaks have been currently underway. The development and occurrence of COPD are tightly correlated with the gut–lung axis, and the microbiome in COPD has a strong anti-inflammatory ability. Studying the intestinal and pulmonary microbiome to explore the alleviation of airway inflammation in COPD could be a novel approach to researching COPD intervention and treatment strategies in the future. In addition, the microbiome and the host's immunological health are tightly intertwined. Therefore, successful identification of microbiome populations may help predict the effectiveness of different treatments. Moreover, early intervention of related microorganisms can be carried out to delay the development of COPD by studying the potential mechanisms connected to the worsening of COPD. More work is needed on the internal relationship between COPD and microbiome to examine and confirm the involvement of advantageous bacterial strains in COPD, optimize the consumption of harmful bacteria, optimize the balance of microorganisms through diet, probiotics and flora transplantation, and find new strategies for prevention or treatment of COPD in the future. Our research revealed the basic scientific knowledge of the microbiome in COPD, timely sorting out and analyzing the current research trends and hot areas in the discipline. It may support the field's ongoing development and assist scholars in better understanding the present general trends in the area.

Data Sharing Statement

The article contains the original findings discussed during the research. The research information used to support this study's results shall be disclosed honestly and without undue reluctance.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The study's authors affirm that there were no financial or commercial ties that might be viewed as having a possible conflict of interest.

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