International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Global Trends in Research Regarding Macrophages Associated with Chronic Obstructive Pulmonary Disease: A Bibliometric Analysis from 2011 to 2022

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Purpose: Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory condition characterized by chronic airway inflammation, where macrophages from the innate immune system may exert a pivotal influence. Our study aimed to summarize the present state of knowledge and to identify the focal points and emerging developments regarding macrophages associated with COPD through bibliometrics.

Methods: Publications regarding research on macrophages associated with COPD from January 1, 2011, to January 1, 2022, were retrieved from the Science Citation Index-Expanded (SCI-E) which is part of the Web of Science database. In total, 1521 publications were analyzed using bibliometric methodology. VOSviewer was used to analyze the annual publications, countries, institutions, authors, journals, and research hotspots.

Results: Based on the bibliometric analysis, publications relating to macrophages associated with COPD tended to increase from 2011 to 2022. The United States was the largest producer and most influential country in this field. Research during the past decade has focused on inflammation in the lungs. Most previous studies have mainly focused on the mechanisms that promote the initiation and progression of COPD. Macrophage-related oxidative stress and immunity, communication between macrophages and epithelial cells, and interventions for acute exacerbations have become the focus of more recent studies and will become a hot topic in the future.

Conclusion: Global research on macrophage-associated COPD has been growing rapidly in the past decade. The hot topics in this field gradually tended to shift focus from "inflammation" to "oxidative stress", "epithelial-cells", and "exacerbations". The significance of macrophages in coordinating immune responses, interacting with other cells, and exhibiting dysregulated capacities has attracted increasing attention to COPD pathogenesis. The adoption of new technologies may provide a more promising and comprehensive understanding of the specific role of macrophages in COPD in the future.

Keywords: macrophages, chronic obstructive pulmonary disease, VOSviewer, research hotspots, bibliometrix

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory condition that is distinguished by persistent limitation of airflow.[1] It is currently the third most fatal disease in the world.[1,2] Existing treatments cannot intrinsically prevent the continuous progression of COPD, and the complicated mechanisms of pathogenesis are still not completely understood.[3]

Macrophages are one of the most abundant immune cells in the innate immune system and are an important bridge connecting innate and adaptive immunity.[4,5] Macrophages are also the primary defense line of the respiratory system against invasion by exogenous pathogens.[6] The main sources of respiratory macrophages are interstitial and alveolar macrophages,

Received: 9 June 2023
Accepted: 21 September 2023
Published: 2 October 2023

with alveolar macrophages (AMs) comprising the predominant cellular component in bronchoalveolar lavage (BAL).[7] At present, macrophages are closely associated with the occurrence and progression of diverse respiratory diseases, including asthma, cystic fibrosis, acute respiratory distress syndrome (ARDS), etc.[8] The main pathogenesis of COPD, including chronic inflammation, oxidative stress, and immunity, involves macrophages from the innate immune system.[8,9] With advances in our understanding of COPD pathogenesis, the relationship between macrophages and COPD has become more prominent. Therefore, research regarding macrophage-associated COPD is attracting increasing attention. At present, it is imperative to fundamentally understand the pathogenesis of COPD and identify targeted treatment measures that focus on the root of the disease, therefore research relating to macrophages may offer a promising breakthrough.

Bibliometric analysis is a scientific method that involves information visualization. It has the characteristics of both quantitative and qualitative analysis and can compare and analyze research data from several aspects and perspectives (countries, institutions, authors, journals, etc.).[10,11] Bibliometrics can also be used to analyze the trends in research hotspots over time and predict future research trends in the current field.[12,13] However, no bibliometric analyses have been performed on macrophage-associated COPD.

The objective of this study was to elucidate the present status of published papers on macrophage-associated COPD over the past 11 years, in order to comprehend the trends and focal points in this area of research. It also aimed to provide new perspectives and a basis for future macrophage-associated COPD research.

Materials and Methods

We used the SCI-expanded Web of Science Core Collection (WoSCC) bibliographic database. Literature retrieval was conducted on a single day (January 5th, 2022). The publication period was set within the range of the last 11 years from 1st January 2011 to 1st January 2022. The search terms were as follows: Topic = (macrophage OR macrophages) AND Topic = (chronic obstructive pulmonary disease OR COPD OR chronic obstructive airway disease). Only original articles and reviews written in English were included.

Data Collection and Cleaning

Two authors (Ye Lu and Xiaoming Zhou) independently conducted a screening of the retrieved literature and ascertained its eligibility. We extracted comprehensive publishing information from the database, including journals, publication year, authors, country/region, number of papers and citations, keywords, affiliations, H-index, and references.

Analysis with VOSviewer

This study constructed bibliometric maps using VOSviewer v. 1.6.10.0 to obtain comprehensive information from the results based on co-authorship, co-citation, and co-occurrence analysis, as previously described.[14] Bibliometric indicators, commonly utilized to represent bibliographic material, encompass the number of papers and citations. Productivity was measured by the number of publications (Np), while impact was represented by the number of citations without self-citations (Nc). These two perspectives are widely recognized as fundamental for evaluating the level of research. The H-index serves as a means of integrating productivity and impact through the establishment of a threshold that links Np with Nc. The Journal Citation Reports' (JCR) most recent iteration yields the impact factor (IF), which is widely recognized as a prominent gauge of medical journal quality and impact. The local citation score (LCS), which is deemed the Nc of an article within a particular field, is a significant indicator of contribution.

Results

An Overview of Publications on Macrophages in COPD

In total, 1760 publications were identified by searching for WoSCC. Keywords, titles, and abstracts of the articles underwent screening and manual filtering. Finally, 1521 publications were analyzed in our bibliometric analysis, excluding 239 articles. A detailed outline of the screening procedure is presented in Figure 1. After screening the publications for original articles and reviews, the final number of COPD-macrophage-related research publications from

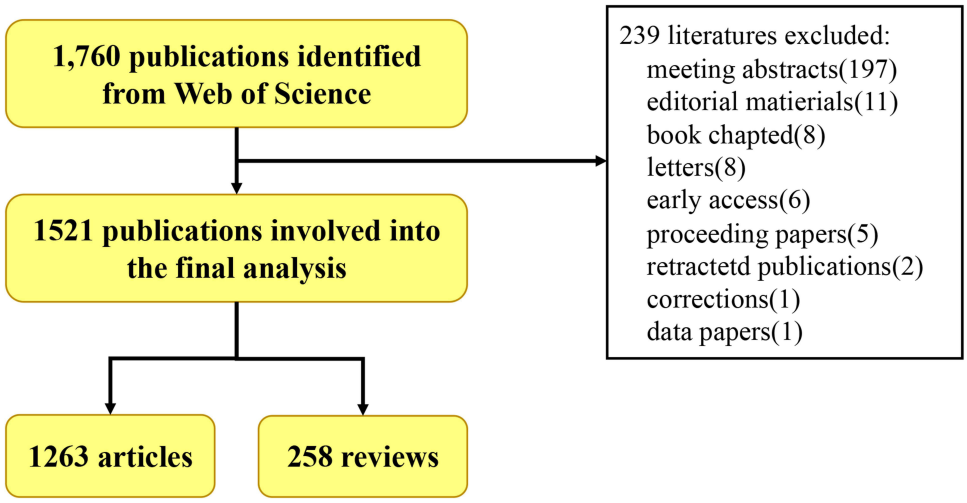

Figure 1 Flowchart of the screening process.

1st January 2011 to 1st January 2022 was 1521. The retrieved articles yielded a total Nc of 34,542 with a mean Nc of 25.18 per article. The collective H-index of all publications was 80.

Historical Overview

The annual number of studies is shown in Figure 2. In general, despite fluctuations over the past 10 years, the number of annual papers rose from 109 in 2011 to 172 in 2021, with a peak in 2021 (Figure 2A). Annual Np remained stable in the majority of countries, however, in China, it experienced a rapid increase (Figure 2B). Therefore, these findings indicate that macrophage-related research has become a hot topic in COPD.

Analysis on Countries/Regions

From a quantitative analysis, the top 10 countries that have published related articles are listed in Table 1. In terms of Np, the United States, China, England, Japan, and Germany are the top five countries/regions; however, concerning the Nc and H-index, the top five countries are the United States, England, Germany, China, and Australia. According to the co-authorship

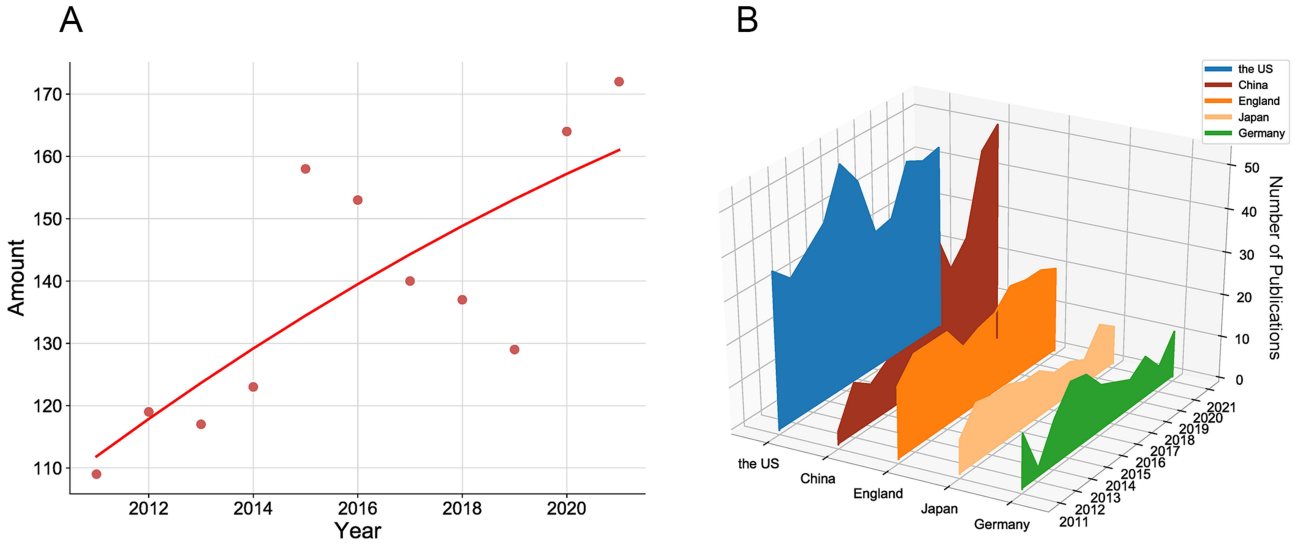

Figure 2 Annual Trend of Research Publication Quantity. (**A**) Curve fitting of the of the total annual growth trend of publications (R^2 = 0.8453). (**B**) The number of publications by year over the past 10 years.

Table 1 Publications in the 10 Most Productive Countries/Regions

Rank	Country/Region	Np	% of (1521)	Nc	H-Index
1	United States	440	28.93%	15,123	62
2	China	277	18.21%	3464	31
3	England	223	14.66%	4665	46
4	Japan	113	7.43%	1846	25
5	Germany	112	7.36%	3736	32
6	Australia	96	6.31%	2914	30
7	Netherlands	78	5.13%	2161	27
8	Italy	76	5.00%	2035	28
9	Canada	71	4.67%	1872	26
10	Sweden	56	3.68%	918	16

Abbreviations: Np, number of publications; Nc, number of citations.

network, the United States exhibited the greatest level of international collaboration with other nations (Figure 3A) (total link strength = 297). The overlay mapping of the country co-authorship revealed that the United States and China have demonstrated significant involvement in the domain of macrophages associated with COPD over the last decade. Additionally, a number of countries that have recently become active in this field were also observed (Figure 3B).

Analysis of Institutions

From a quantitative analysis, the top 10 institutions that have published related articles are listed in Table 2. The top five institutions based on the Np were Imperial College (England), University of Manchester (England), US Department of Veterans Affairs (the United States), Veterans Health Administration (the United States), and Pennsylvania Commonwealth System of Higher Education (the United States). The results showed that institutions from the United States and England have contributed the most to the field of macrophages associated with COPD, in the last 11 years.

Analysis on Authors

The analysis results on the top 10 authors with published papers are listed in Table 3. The authors with the highest number of publications, namely Singh D (University of Manchester, Manchester, England), Hodge S (University of Adelaide, Adelaide, SA, Australia), Barnes PJ (Imperial College, London, England), Donnelly LE (Imperial College, London, England), and Vlahos R (University of Melbourne, Victoria, Australia), are nearly identical to the top five

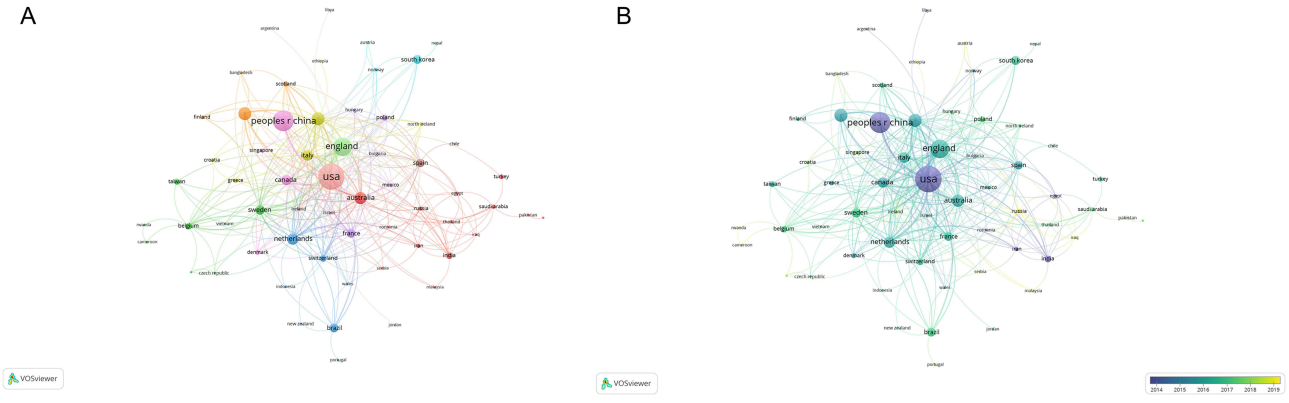

Figure 3 The mapping on co-authorship counties/regions networks. (**A**) Counties/regions co-authorship network visualization map. Clusters are grouped by the frequency of shared co-occurrence terms that represent each country. Closely related terms are grouped into the same cluster with the same color. The size of each circle represents the number of publications a country has produced, with more publications generating a larger circle. The line between the two points in the figure represents those two countries/regions had established a similar relationship. The thicker the line, the closer the link between the two countries/regions. (**B**) Countries/regions co-authorship overlay visualization map. The color of each node is based on its average publication year. Counties/regions in yellow appeared later than those in blue.

Table 2 Publications in the Top 10 Most Productive Institutions

Rank	Institutions	Country	Np	Nc	H-Index
1	Imperial College	England	90	4151	34
2	University of Manchester	England	53	1556	22
3	US Department of Veterans Affairs	United States	52	1735	22
4	Veterans Health Administration	United States	50	1707	22
5	Pennsylvania Commonwealth System of Higher Education	United States	42	1357	17
6	University of Groningen	Netherlands	41	1413	20
7	Astrazeneca	Sweden	39	1019	16
8	Harvard University	United States	39	1352	20
9	University of California System	United States	38	1635	19
10	Wythenshawe Hospital Nhs Foundation Trust	England	38	875	20

Abbreviations: Np, number of publications; Nc, number of citations.

Table 3 The Top 10 Authors with the Most Publication

Rank	Author	Country	Np	Nc	H-Index
1	Singh, D	England	46	1009	20
2	Barnes, PJ	England	42	2856	27
3	Hodge, S	Australia	21	505	16
4	Donnelly, LE	England	20	634	13
5	Vlahos, R	Australia	17	629	14
6	Chung, KF	England	16	442	12
7	Lea, S	England	16	376	11
8	Bozinovski, S	Australia	15	604	13
9	Hodge, G	Australia	15	334	11
10	Zhang, Y	China	15	137	6

Abbreviations: Np, number of publications; Nc, number of citations.

authors in terms of H-index and Nc. It is evident that despite the prolific publication of articles by researchers from the United States, Japan, and Germany, they have not attained a position within the top 10 with a commendable H-index.

Of the 10 most co-cited authors, Barnes PJ (Imperial College, London, England) ranked first, with 1080 citations, followed by Hodge S (University of Adelaide, Adelaide, SA, Australia) (Table 4). The co-citation authors' networks are shown in Figure 4. The co-citation analysis of authors offers a comprehensible depiction of the scholarly standing and impact of researchers within the given research domain.[15,16] Barnes PJ (Imperial College, London, England) had the highest, Nc, co-citations, and H-index.

Analysis of Journals

As shown in Table 5, the top 10 journals are listed. Plos One had the largest Np in the macrophage-associated COPD field (81 publications, IF: 3.75). Respiratory Research (66 publications, IF: 7.16) and International Journal of Chronic Obstructive Pulmonary Disease (61 publications, IF: 2.89) ranked second and third, respectively. Around 30% of the scholarly articles (460 publications) were disseminated in the foremost 10 academic journals. With an Nc of 2212 and an H-index of 27, Plos One has emerged as the leading contributor to research in this field over the past 11 years. European Respiratory Journal, American Journal of Respiratory and Critical Care Medicine, and Chest had the highest IF of 33.80, 30.53, and 10.26, respectively. European Respiratory Journal is an influential journal for research regarding macrophages associated with COPD.

Analysis of LCS

Figure 5 displays the LCS per year for the top 10 papers. Notably, a significant advancement in papers with a high LCS occurred post-2020. Table 6 and Table 7 present the LCS per year for the top 10 papers. Among the top-cited

Table 4 The Top 10 Co-Citation Authors

Rank	Author	Institutions	Country	Nc	Total Link Strength
1	Barnes, PJ	Imperial College	England	1080	13,517
2	Hodge, S	University of Adelaide	Australia	442	5385
3	Hogg, JC	St. Paul's Hospital, and Department of Medicine	Canada	346	4667
4	Churg, A	St. Paul's Hospital, and Department of Medicine	Canada	279	4767
5	Rahman, I	University of Rochester Medical Center	United States	228	3377
6	Shapiro, SD	University of Pittsburgh	United States	213	2978
7	Sethi, S	Veterans Health Administration	United States	210	2868
8	Di stefano, A	Istituti Clinici Scientifici Maugeri	Italy	208	3557
9	Berenson, CS	State University of New York at Buffalo School of Medicine	United States	199	3459
10	Ito, K	Imperial College	England	195	2974

Abbreviation: Nc, number of citations.

publications, there were more reviews than articles. In the first 31 top-cited publications, only 10 were articles and 21 were reviews.

A paper written by Xue in 2014 ranked first in terms of the LCS (LCS =1079), most likely because it was groundbreaking and elaborated the transcriptional control of human macrophage activation to diverse stimulus signals and found the biology of alveolar macrophages in COPD, an unexpected absence of inflammatory signatures.[17] This study sheds light on the regulation of macrophage activation in health and disease.[17] In a second highly cited article

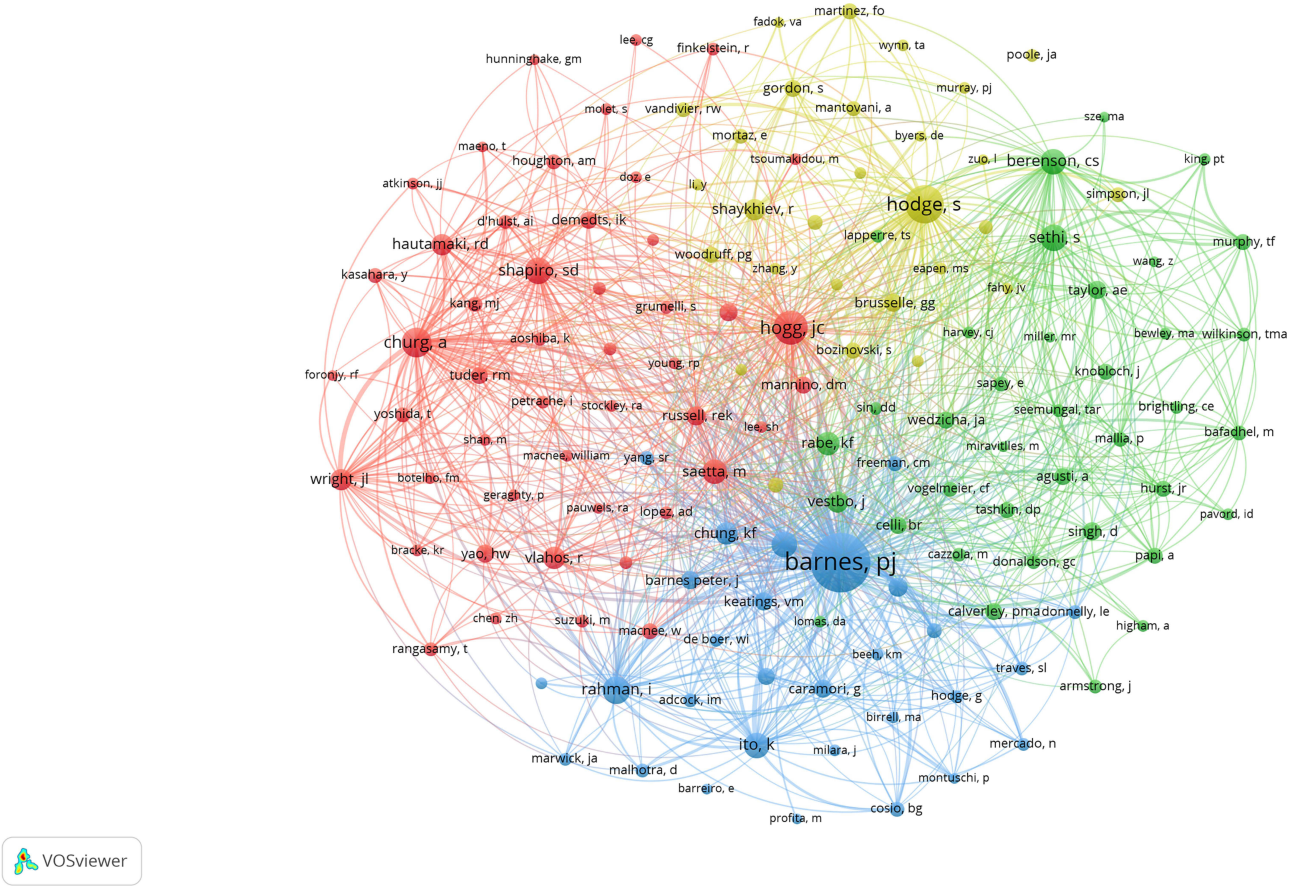

Figure 4 The mapping on co-cited authors networks. The relevance of authors is determined by the number of times that their articles are referenced by the same article. The same color represents authors who are within the same topic of interest. The size of each circle represents the number of citations of the author, with more citations generating a larger circle. The thickness of the connecting line indicates the strength of the link.

Table 5 The Top 10 Journals with the Most Publications

Rank	Journal	Np	Nc	H-Index	IF (2021)
1	Plos One	81	2212	27	3.75
2	Respiratory Research	66	1226	22	7.16
3	International Journal of Chronic Obstructive Pulmonary Disease	61	1051	18	2.89
4	American Journal of Physiology-Lung Cellular and Molecular Physiology	50	1134	20	6.01
5	American Journal of Respiratory Cell and Molecular Biology	47	1273	20	7.75
6	Scientific Reports	38	625	14	5.00
7	Chest	31	1707	20	10.26
8	European Respiratory Journal	30	1114	20	33.80
9	Frontiers in Immunology	29	789	13	8.79
10	American Journal of Respiratory and Critical Care Medicine	27	1025	21	30.53

Abbreviations: Np, number of publications; Nc, number of citations; IF, impact factor.

written by Roy MG in 2014, mouse Muc5b (but not Muc5ac) was required for mucociliary clearance; a decrease in Muc5b, which is common in most COPD patients, results in apoptotic macrophage accumulation and impaired phagocytosis, leading to chronic infection by multiple bacterial species.[18] In addition to this, the 3rd and 5th highly cited articles also focused on bacterial clearance and pulmonary antibacterial and antiviral defenses involving macrophages.[19,20] The 4th study sought to ascertain the potential mechanism of azithromycin in a randomized, double-blind, placebo-controlled trial.[21] The article revealed that the administration of azithromycin resulted in an elevation of bacterial metabolites, such as glycolic acid, indol-3-acetate, linoleic acid, glycolic acid, and indol-3-acetate, while simultaneously attenuating the ex vivo production of proinflammatory cytokines by alveolar macrophages stimulated with LPS. The 6th article indicated that smoking is linked to genome-wide changes in DNA methylation at the aryl hydrocarbon receptor repressor (AHRR) in alveolar macrophages, which have functional significance. Additionally,

Figure 5 The yearly number of local citations of papers with high local citations (LCS). The size and colors of the circle represent the LCS of papers.

Table 6 The Top 10 Cited Articles

Rank	Title	Year	Citations	Journal	IF (2021)
1	Transcriptome-based network analysis reveals a spectrum model of human macrophage activation	2014	1079	Immunity	43.47
2	Muc5b is required for airway defence	2014	406	Nature	69.50
3	Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model	2015	232	Plos One	3.75
4	Randomised, double-blind, placebo-controlled trial with azithromycin selects for anti-inflammatory microbial metabolites in the emphysematous lung	2016	228	Thorax	9.1
5	Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model	2011	206	Sci Transl Med	19.32
6	Coordinated changes in AHRR methylation in lymphoblasts and pulmonary macrophages from smokers	2012	182	Am J Med Genet B Neuropsychiatr Genet	3.36
7	Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type 1 interleukin-33-dependent response to infection	2015	174	Immunity	43.47
8	IL-17RA is required for CCL2 expression, macrophage recruitment, and emphysema in response to cigarette smoke	2011	156	Plos One	3.75
9	A new short-term mouse model of chronic obstructive pulmonary disease identifies a role for mast cell tryptase in pathogenesis	2013	148	J Allergy Clin Immunol	14.29
10	Decreased histone deacetylase 2 impairs Nrf2 activation by oxidative stress	2011	130	Biochem Biophys Res Commun	3.32

Abbreviation: IF, impact factor.

Table 7 The Top 10 Cited Reviews

Rank	Title	Year	Citations	Journal	IF
1	Inflammatory mechanisms in patients with chronic obstructive pulmonary disease	2016	507	J Allergy Clin Immunol	14.29
2	New insights into the immunology of chronic obstructive pulmonary disease	2011	455	Lancet	202.73
3	Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease	2013	411	J Allergy Clin Immunol	14.29
4	Oxidative stress in COPD	2013	347	Chest	10.26
5	Azithromycin: mechanisms of action and their relevance for clinical applications.	2014	254	Pharmacol Ther	13.4
6	Cellular and molecular mechanisms of chronic obstructive pulmonary disease	2014	249	Clin Chest Med	4.97
7	Mechanistic links between COPD and lung cancer	2013	249	Nat Rev Cancer	69.8
8	Cellular and molecular mechanisms of asthma and COPD	2017	180	Clin Sci (Lond).	6.88
9	Modulation of macrophage efferocytosis in inflammation	2011	180	Front Immunol	8.79
10	Interleukin-18: Biological properties and role in disease pathogenesis	2018	160	Immunol Rev	10.98

Abbreviation: IF, impact factor.

pathway analysis found alterations in inflammation-related processes.[22] The 7th article found that smoke promotes an IL-33-dependent proinflammatory response by enhancing ST2 expression in macrophages, in COPD.[23] The 8th article focused on immunological mechanisms: inhalation of cigarette smoke was found to possess a strong capacity as a Th17 adjuvant, with the activation of IL-17RA signaling being a necessary component for the recruitment of macrophages, CCL2, and the development of tissue emphysema.[24] The 9th article focused on the mast cells (MCs) transporter in the pathogenesis of COPD. Mouse mast cell protease (mMCP)-6 contributes to macrophage aggregation and inflammation in mice with experimental COPD.[25] The 10th article revealed that diminished HDAC2 activity in individuals with COPD may lead to heightened Nrf2 acetylation, decreased Nrf2 stability, and compromised antioxidant defense in both epithelial cells and macrophages.[26] Amongst these studies, three involved humans, seven involved animals, and nine

Figure 6 The mapping on keywords of research of macrophages associated with chronic obstructive pulmonary disease over the past 11 years. (**A**) The 132 keywords, which occurred more than 19 times among 5666 keywords, were divided into five clusters by different colors: cluster 1: red, cluster 2: green, cluster 3: blue, cluster 4: yellow, and cluster 5: purple. The size of the nodes represents the frequency of occurrences. The color of an item is determined by the cluster to which the item belongs. The thickness of the connecting line indicates the strength of the link. (**B**) Visualization of keywords according to the average publication year. Keywords in yellow appeared later than those in blue.

involved cells. Most research has focused on mechanisms, such as activation and aggregation of macrophages, promoting initiation and progression of COPD.

Among the top 10 cited reviews, the 1st,[9] 2nd,[4] 4th,[27] 6th,[28] 9th,[29] and 10th[30] reviews focused on the mechanism of COPD involving macrophages and other inflammatory cells, while the 3rd[31] and 5th[32] publications reviewed the treatment hotspots, namely corticosteroid resistance and azithromycin. Connections of COPD with other diseases, such as lung cancer and asthma, were reviewed in the 7th[33] and 8th[34] publications. The 7th highest cited review referred to inflammation, increased oxidative stress in macrophages, and the increased secretion of matrix metalloproteinase 9 (MMP-9) from macrophages, which pertained to the close relationship between COPD and lung cancer.[33] The 8th highest cited review expounded on the differences and relationship between COPD and asthma with regard to the cellular and inflammatory mechanisms.[34] The pro- and anti-inflammatory effects and reduced phagocytosis of macrophages were observed in both severe asthma and COPD.

Analysis of Research Hotspots

Furthermore, VOSviewer was utilized to analyze the keywords extracted from the titles and abstracts of the 1521 papers, in addition to the search terms (Figure 6). The 132 keywords, which occurred more than 19 times among the 5666 keywords, were divided into five clusters: cluster 1 primarily centred on the activation, differentiation, and polarization of macrophages; cluster 2 primarily focused on infection, exacerbation of COPD, and macrophage phagocytosis; cluster 3 mainly focused on airway inflammation and emphysema; cluster 4 mainly focused on animal models; and cluster 5 mainly focused on in vivo mechanisms involving immunity and autophagy (Figure 6A). The most common keywords were "inflammation", "expression", and "alveolar macrophages", except for "obstructive pulmonary disease and COPD". Figure 6B illustrates the division of the colors of all keywords through the utilization of VOSviewer, based on the average publication year (APY). Over time, the evolution of research has resulted in a shift from centralized to dispersed research hotspots. During the initial studies conducted in this field, the hotspots were animal models, receptors, neutrophils, inhibition, and induction. Recent hotspots with a relatively high frequency of occurrence were oxidative stress, epithelial cells, NF-κB, exacerbation, phagocytosis, and cigarette smoke.

Discussion

The present research utilized bibliometric analysis to examine the emerging trends and focal points in research on macrophages associated with COPD, spanning the years 2011 to 2022, in the SCI-expanded database through the utilization of VOSviewer software. Bibliometric study is a valuable approach to illustrate the development of scientific knowledge and its structural connections. This method has been extensively employed to monitor research progress.[35,36]

In the visualization techniques, networks are utilized to represent various parameters by using colors, circles of varying sizes, font sizes, and line thicknesses. In the keywords' overlay visualization map, the colors correspond to the publication years. The results suggest that future research in the field of macrophage-associated COPD may focus on oxidative stress, epithelial cells, NF-κB, exacerbation, and related areas, as these topics are likely to gain popularity.

Notably, there was a decline in the number of publications from 2016 to 2019. Subsequently, an obvious rise in publication numbers was observed from 2019 onwards. This is an interesting phenomenon due to complex factors. Besides this decline, it was also observed that the top articles and reviews on macrophages and COPD were mainly published before 2016. A similar trend in publication numbers across the United States, China, Japan, and Germany was also evident. As a result, the overall trend showed a decline from 2016 to 2019. However, following a comprehensive bibliographic analysis of the literature on macrophage-related studies, a steady upward trend in publication numbers can be observed, commencing from the year 2019. The year 2021 exhibited the publication peak with the most publications. Thus macrophage research hotspots in 2019 might stimulate the further growth. In addition, the fitted curve analyses show that the total number of annual global publications regarding macrophages associated with COPD is still a growing trend. This indicates that the field is receiving increasing attention from researchers. Particularly after 2020, the upward trend was remarkable, most likely due to the breakthrough of papers with a high LCS.[4,9,17–19] An increasing number of studies have primarily focused on COPD pathogenesis mediated by macrophage polarization, apoptosis, autophagy, and dysfunction.[37–39] Consequently, through cell-cell interaction, tissue injury-based pulmonary emphysema, airway inflammation, bronchial epithelium remodelling, and mucus impairment were initiated and programmed to lead to COPD pathogenesis. Furthermore, the application of new technologies that investigate the functional role of macrophages and, in particular, the combination of cell types as well as single-cell transcriptomics and proteomic approaches, are creating new opportunities to understand and clarify the pathophysiology and the clinical heterogeneity of COPD.[40–44]

The results for the top 10 countries/regions with the most extensive literature regarding macrophages associated with COPD showed global distribution. The United States holds a leading position in the field of macrophage-associated COPD with the highest Np, Nc, and H-index, as well as the most international cooperation, compared to other countries/regions, and also carried out research in this field earlier. The current study shows that China is one of the earliest and most productive countries in the field of macrophages associated with COPD. However, it should be noted that the Nc and H-index of papers from China are relatively low compared to those from England, with less internal cooperation. England ranked 3rd when measuring the Np. However, in terms of the Nc and H-index, it was placed 2nd, following the United States.

The majority of the top 10 most productive institutions were affiliated with the United States, exhibiting a relatively high Nc. Notably, three of the top 10 most productive institutions were associated with England; Imperial College and University of Manchester ranked 1st and 2nd, corresponding to the productivity of the countries/regions. Imperial College has the highest Np, Nc, and H-index of publications in the field of macrophages associated with COPD, making it the top institution with high productivity and influence in this field. Professor Barnes, PJ who has the highest Nc, H-index, and the most co-citation in this bibliometric analysis, is from Imperial College London.

The authors with the highest Np and relatively high H-index and Nc were mostly from England and Australia, indicating that authors from these countries/regions had a greater influence in the field of macrophages associated with COPD. Professor Barnes, PJ, with the highest Nc, H-index, and co-citations in the field of macrophage-associated COPD, was from England and is a leading expert in the field of COPD and a member of the GOLD core expert group. Five of the top 10 cited reviews,[9,27,28,31,34] in the current bibliometric analysis were written by Barnes, PJ, who has focused his researches on the cellular and molecular mechanisms of chronic airway diseases, particularly inflammatory and oxidative stress pathways. In his reviews, he elucidated that the significant role of macrophages in COPD is the orchestration of airway inflammation and macrophages are activated and significantly increased in COPD presenting as different phenotypes to secret cytokines, chemokines, and proteases, a greater chemotactic response, and reduced phagocytosis to initiate and mediate inflammation and oxidative stress response.[9,27,28,31,34]

Amongst the 10 SCI-expanded journals with the highest Np, 8 had an IF $\geq$ 5.0, and 3 had an IF>10.0, indicating relatively high quality in this field. The European Respiratory Journal has the highest IF. Plos One has a higher

publication volume and larger Nc, as well as the highest H-index in macrophages associated with COPD, with two of the top 10 cited articles published in this journal.

The Nc holds significant value as an indicator in bibliometric studies, as it serves to reflect the level of importance that literature holds in academic research.[15] Overall, 64.5% (20/31) of the top-cited papers were reviews, describing the current research results and debate points and proposing directions for future research; this indicated hotspots of interest in the area and the urgent desire of researchers to understand the current research status of macrophages associated with COPD in recent years. Five of the top 10 articles and six of the top 10 cited reviews were related to mechanisms that promote the initiation and progression of COPD, highlighting the importance of macrophage activation and accumulation in COPD pathogenesis.[4,9,22–28,33,34] Macrophages are also significant contributors to the crosstalk between COPD and other diseases, such as asthma or cancer.[33,34]

The present bibliometric analysis revealed that the most common keywords were "inflammation" and "expression", which means that macrophage-related inflammation has been highly focused in the last decade, in this research field. Inflammation is a crucial aspect of COPD pathogenesis, in which innate immune macrophages play an important role via the release of numerous inflammatory factors and activation of other cell types. In addition to this, systemic inflammation is another prominent characteristic of COPD pathogenesis, which is associated with the decreased phagocytosis of macrophages and impaired ability to resolve inflammation.[9]

Over time, the increased focus in the field of macrophages associated with COPD was dispersed and switched to "oxidative stress", "epithelial-cells", and "exacerbations". Cigarette smoke (CS) is a primary exogenous origin of reactive oxygen species (ROS) and/or nitrogen species (RNS).[45,46] In addition to this, CS can induce macrophages, epithelial cells, and other cells in the lungs to produce numerous endogenous ROS and RNS.[27,47] The augmented levels of ROS within macrophages additionally contribute to the involvement of oxidative stress in the inflammatory response through the activation of the nuclear transcription factor NF-κB.[27,47] Oxidants can dislocate I-κB, the repressor protein of NF-κB, and activate NF-κB, thus initiating the transcription of inflammatory factors.[48] Consequently, there is a rise in the recruitment of inflammatory cells, resulting in the generation of ROS and an elevation in the burden of oxidative stress. Another aspect of oxidative stress in COPD is impaired endogenous antioxidant defense.[45,47] Glutamylcysteine ligase is a key enzyme for the synthesis of glutathione (GSH), an important antioxidant that has been found to be decreased in the macrophages of smokers.[27]

Another emerging area of focus in this bibliometric analysis was "epithelial-cells". Five of the top-cited reviews emphasized that COPD is a complex pathophysiological process involving the common participation and interaction of multiple cell types.[4,9,27,28,34] Epithelial cells are important structural cells of the respiratory system and are associated with local fibrosis of the small airways and emphysema in COPD.[9] Moreover, epithelial cells, that participate in inflammation, are the main source of ROS and antioxidants such as GSH.[49] Therefore, additional research is needed to explore the interactions between macrophages and epithelial cells. Three primary modes of interaction were identified, including the direct impact of the inflammatory medium. Macrophages express inflammatory cytokines such as IL-1β and TNF-α, which can augment the expression of IL-6 in epithelial cells.[50] In the second mechanism, gap junction channels (GJCs) might be involved in intercellular communication, via which the two types of cells interact.[51,52] In the third mechanism, extracellular vesicles (EVs), which mainly refer to apoptotic bodies, the budding of the cell membrane, and exosomes, are the media used for communication between the lung epithelial cells and macrophages; they need to be studied further, and may lead to improved knowledge regarding the pathogenesis of COPD.[47,53,54]

In addition to this, "exacerbation" is also a newly emerging research hotspot in this field, according to our study. Six of the top 10 cited reviews[4,9,27,28,32,34] and three of the top 10 cited articles[20,21,23] involved acute exacerbation of COPD (AECOPD). The occurrence of AECOPD is linked to an unfavourable prognosis, reduced quality of life, and elevated mortality rates.[20,55] Therefore, effective intervention measures are urgently required. Viral infections and periodic bacterial (*Haemophilus influenza, Pseudomonas aeruginosa*, etc.) infections caused by the impaired phagocytosis of macrophages are the main causes of acute COPD exacerbations.[20] Oxidative stress is closely related to impaired macrophage phagocytosis in COPD;[45] oxidative stress can activate intracellular RhoA by altering the cytoskeletal reorganization and impairing the phagocytosis of macrophages.[27] Disruption of the important antioxidant regulator, Nrf2, and its signalling pathway in COPD is related to a decrease in the anti-bacterial phagocytosis of macrophages.[20]

The carbonylation of tissue proteins, caused by extracellular oxidative stress, hinders the phagocytic function of macrophages by competing with their pattern recognition receptors (PRRs).[27] In addition to this, oxidative stress can reduce mannose-binding lectin (MBL), which is associated with a decrease in the phagocytosis of macrophages to apoptotic cells and bacteria.[47,56] The decreased phagocytosis of macrophages results in increased bacterial colonization in the lower airways, which is an important risk factor for frequent AECOPD.[57] The current treatment for AECOPD is still broad because of the coexistence of several complex mechanisms and the heterogeneity of the disease, and individualized treatment regimens are an area of interest.[58,59] Several pharmacological approaches for the prevention of AECOPD have shown promising results,[60] such as triple therapy combinations, phosphodiesterase-4 inhibitors, macrolide antibiotics, biologic agents (such as IL-5 and its receptor), and statins. Azithromycin is a promising drug for AECOPD prevention; it has an anti-infection role and also improves macrophage function by increasing phagocytosis and shifting polarization to the alternative/anti-inflammatory M2-phenotype.[32,47,57,61] A real-world retrospective study showed that long-term azithromycin use in patients with GOLD D reduced exacerbations of COPD.[62] Moreover, GOLD 2022 described that azithromycin can reduce the risk of exacerbations in patients prone to them.[63] A systematic review and meta-analysis involving 11 randomized controlled trials (RCTs) also demonstrated that prophylactic azithromycin treatment had a noteworthy impact on reducing the frequency of AECOPD.[64] The significance of azithromycin needs to be further evaluated, and its side effects (digestive symptoms, hearing loss, arrhythmia, etc.), bacterial resistance, and the benefit of treatment for longer than a year need to be considered.[58] Despite the lack of success in utilizing singular antioxidants for the treatment of AECOPD, it is expected that future studies relating to antioxidants will improve the treatment of AECOPD.[45]

Given the close association between oxidative stress, inflammation, and macrophage function, interventions of the interaction nodes for each or multiple pathways of the mechanism of COPD may improve the prognosis of COPD. Although the uniform presentation of COPD is incompletely reversible airway obstruction mediated by airway inflammation,[65] there is a considerable degree of heterogeneity and phenotypic complexity within the disease. This is evident through the presence of various manifestations such as emphysema, chronic mucus hypersecretion, and comorbid conditions including asthma, sleep apnea, coronary artery disease, and osteoporosis, each requiring specific treatment approaches.[66,67] Besides the various risk factors and exacerbation precipitating factors, pathogenesis of various phenotypes is shown briefly via the interaction nodes. Interventions involving or targeting these interaction nodes hold potential for future therapies in COPD, specifically for the optimal allocation of a precision medicine approach to effectively treat individuals with distinct phenotypes.[68]

This study had several limitations. First, the study did not incorporate non-English articles, which could have resulted in a degree of bias. Second, although the WoSCC database is comprehensive and large, significant papers from other databases may have been missed. Finally, the study has a certain hysteretic quality, because new significant articles are published quickly and research trends may evolve daily.

Conclusion

Global trends in research regarding macrophage-associated COPD have increased rapidly over the last decade. Recently, there has been a surge of interest in investigating the mechanisms underlying COPD, with particular emphasis on a cell-specific role or repertoire of macrophages. Lung macrophages, including resident alveolar and interstitial macrophages, as well as blood monocytes, have demonstrated their ability to exploit their prevalence and strategic localization to orchestrate immune responses and interact with other effecting cells such as epithelial cells or neutrophils. Consequently, this contributes to the progression of disease through alterations in macrophage phenotypes and their dysregulated capacities. Exploring these areas has the potential to facilitate the development of therapies that specifically target phenotypes or individuals, revealing the therapeutic effects. Furthermore, advances in new technologies, such as single-cell transcriptomics and proteomic approaches, have enabled the investigation of cell-specific roles of macrophages and cell-cell interactions. These advances are illuminating new insights into understanding COPD pathogenesis and heterogeneous phenotypes.

Acknowledgments

This research was supported by National High Level Hospital Clinical Research Funding (2022-NHLHCRF-LX-01), the Elite Medical Professionals project of China-Japan Friendship Hospital (No. ZRJY2021- BJ08), the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2020-PT320-001). Funding information for this article has been deposited with the Crossref Funder Registry.

Disclosure

The authors report no conflicts of interest in this work.

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