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ORIGINAL RESEARCH

Global Research Trends in Comorbidity Between Chronic Obstructive Pulmonary Disease and Gastro-Oesophageal Reflux Disease: A Bibliometric Study

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Background: Chronic obstructive pulmonary disease (COPD) and gastro-oesophageal reflux disease (GERD) frequently coexist and exert bidirectional effects through inflammatory, mechanical, and neurogenic pathways. However, a systematic and integrative summary of global research trends and underlying mechanisms in this field remains lacking.

Methods: Relevant publications on the comorbidity of COPD and GERD published from database inception to 2025 were retrieved from the Web of Science Core Collection. After rigorous screening, bibliometric and visualisation analyses were conducted using VOSviewer and CiteSpace to evaluate publication trends, country and institutional distributions, author collaboration networks, and keyword evolution. Highly cited papers were further examined, and recent mechanistic studies were integrated to explore the pathological connections and clinical implications of the two diseases.

Results: A total of 208 relevant publications were included. The global number of publications has shown a continuous upward trend, with the United States and Europe leading in both productivity and academic influence, while Asian countries have demonstrated rapid growth. Research hotspots have shifted from epidemiological and symptom-based studies towards mechanistic investigations such as non-acid reflux, microaspiration, systemic inflammation, and Mendelian randomisation. Highly cited works, including Hurst JR (2010, NEJM) and Vogelmeier CF (2017, ERJ), have established the theoretical foundation for COPD exacerbation and comorbidity management. Mechanistically, GERD may exacerbate COPD through acid and bile reflux, oesophago–bronchial reflexes, and systemic inflammatory responses, whereas COPD-related respiratory mechanics alterations and chronic inflammation may in turn promote reflux development.

Conclusion: Research on COPD–GERD comorbidity is currently evolving from clinical observation towards molecular and genetic mechanisms, reflecting a clear interdisciplinary trend. Multi-omics studies and integrated management strategies are expected to promote more precise disease phenotyping and personalised treatment. This study elucidates the developmental trajectory of COPD–GERD comorbidity research and provides a theoretical basis and research direction for the advancement of precision respiratory medicine.

Keywords: chronic obstructive pulmonary disease, gastro-oesophageal reflux disease, comorbidity, bibliometric analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading chronic diseases worldwide in terms of morbidity and mortality. It is characterised by persistent respiratory symptoms and airflow limitation resulting from airway and/or alveolar abnormalities.[1] The disease imposes a significant burden on public health systems and socioeconomic resources, as well as on patients themselves.[2] Gastro-oesophageal reflux disease (GERD) is a common upper gastrointestinal disorder, primarily characterised by the reflux of gastric contents into the oesophagus, causing symptoms or complications such as oesophagitis

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and aspiration.[3] In recent years, increasing attention has been paid to the comorbidity between COPD and GERD,[4] as the two conditions share a high prevalence and exhibit a complex bidirectional relationship.

Studies have shown that the prevalence of GERD among patients with COPD is significantly higher than in the general population. GERD is considered to increase both the frequency and severity of acute exacerbations of COPD (AECOPD), accelerate the decline in lung function, and markedly reduce quality of life.[5] Conversely, the pathophysiological features of COPD such as chronic cough, elevated intrathoracic pressure, flattened diaphragm, and the use of bronchodilators may aggravate gastro-oesophageal reflux. Thus, there exists a complex bidirectional relationship between COPD and GERD, involving multiple mechanisms such as mechanical alterations, inflammatory responses, and neural regulation. Moreover, microaspiration of gastric contents and vagally mediated bronchoconstrictive reflexes have been proposed as key pathways underlying their mutual influence.[6,7]

Although both clinical and basic research on the relationship between COPD and GERD have been increasing, current evidence remains fragmented and inconsistent. Previous studies have primarily focused on pathophysiological mechanisms, pharmacological interventions (such as proton pump inhibitors), or the effect of GERD on COPD exacerbations, but a systematic evaluation of the overall knowledge structure, academic landscape, and emerging hotspots in this field is still lacking. With the growing number of publications in this area, a quantitative analysis of publication trends, research collaboration, and thematic evolution has become increasingly necessary.

Therefore, the present study aimed to perform a systematic bibliometric and visualisation analysis of publications related to COPD–GERD comorbidity from database inception to 2025, based on the Web of Science Core Collection (WoSCC). Through an integrated analysis of publication trends, major countries and institutions, key authors, and keyword clustering, this study sought to: (1) delineate the overall development trajectory and research structure of this field; (2) identify principal research themes and emerging hotspots; and (3) provide directional insights for future interdisciplinary collaboration and translational research.

This study is expected to present a comprehensive overview of the global academic landscape of COPD–GERD comorbidity research, offering data-driven support and conceptual insights for researchers and clinicians concerned with the interaction between the respiratory and digestive systems.

Materials and Methods

Data Collection

This study was conducted based on the WoSCC database for literature retrieval and analysis. To ensure the authority and reproducibility of the data, the search period was set from the inception of the database to 30 September 2025.

The search strategy was designed according to the Topic (TS) field, combining standard medical subject terms and common variants for COPD and GERD. The specific search formula was as follows: TS = (Chronic obstructive pulmonary disease OR COPD) AND TS = (gastroesophageal reflux disease OR GERD OR reflux esophagitis OR Barrett's oesophagus OR acid reflux).

The document type was limited to Articles and Reviews, with no language restrictions applied. Conference abstracts, book chapters, editorial materials, and non–peer-reviewed publications were excluded. All retrieval processes were completed in October 2025, and the searches and screening were independently performed by two researchers to ensure data consistency.

The process of data collection and analysis is illustrated in Figure 1.

Analytical Method

This study employed a combination of bibliometric software tools for comprehensive analysis. Bibliometrix was used to examine the temporal evolution of publications, as well as the distribution of countries, institutions, authors, and journals, and to perform thematic evolution analysis. VOSviewer (version 1.6.20) was applied for co-occurrence and co-citation network visualisation to identify collaborative clusters and research associations. CiteSpace (version 6.3.R1) was used to conduct co-citation analysis and burst detection, thereby revealing emerging trends and shifts in research focus. Finally, Microsoft Excel was utilised to organise and summarise the relevant analytical data.

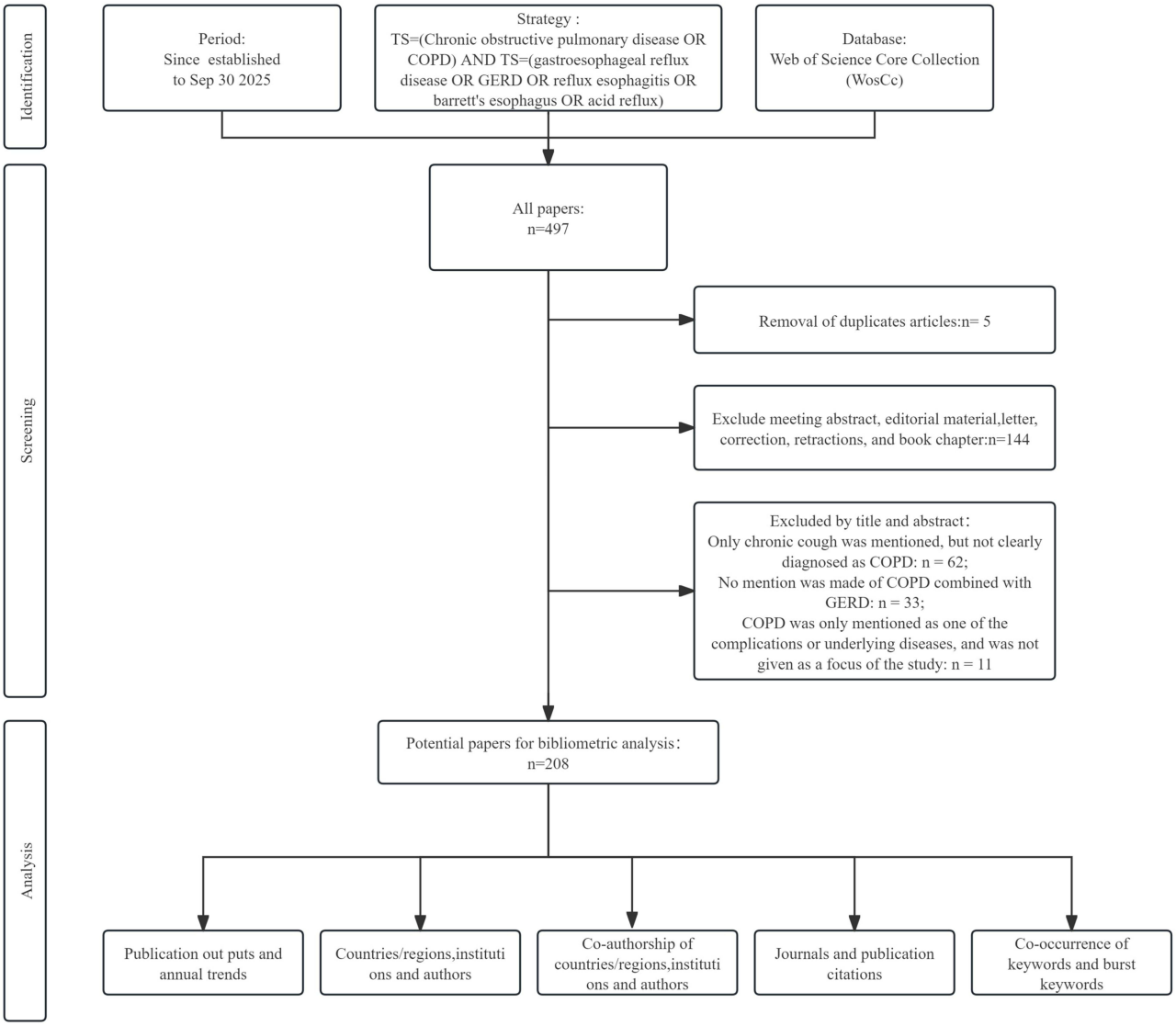

Figure 1 Search strategy and data processing.

Results

Overall Characteristics of the Literature

A total of 497 publications related to the comorbidity of COPD and GERD were retrieved from the WoSCC. After screening, 208 articles were included for analysis (Figure 1). The annual publication trend demonstrated a continuous increase in research output (Figure 2). Studies on COPD–GERD comorbidity first appeared in 2004, followed by a gradual rise in the number of publications. Between 2013 and 2016, the research output increased rapidly, indicating growing academic attention to the intersection between the respiratory and digestive systems. Since 2016, the number of publications has stabilised, reflecting a consolidation phase in this research field.

Analysis of Major Contributing Countries and Institutions

A total of 42 countries or regions participated in research on COPD-GERD comorbidity. The top three countries in terms of publication volume were the United States, China, and the United Kingdom (Figure 3A). Table 1 presents the ten countries with the highest number of publications: the United States ranked first with 60 papers, followed by China (39), the United Kingdom (26), Japan (22), and Spain (18). Although the United States had the greatest total citation count, the average citations per

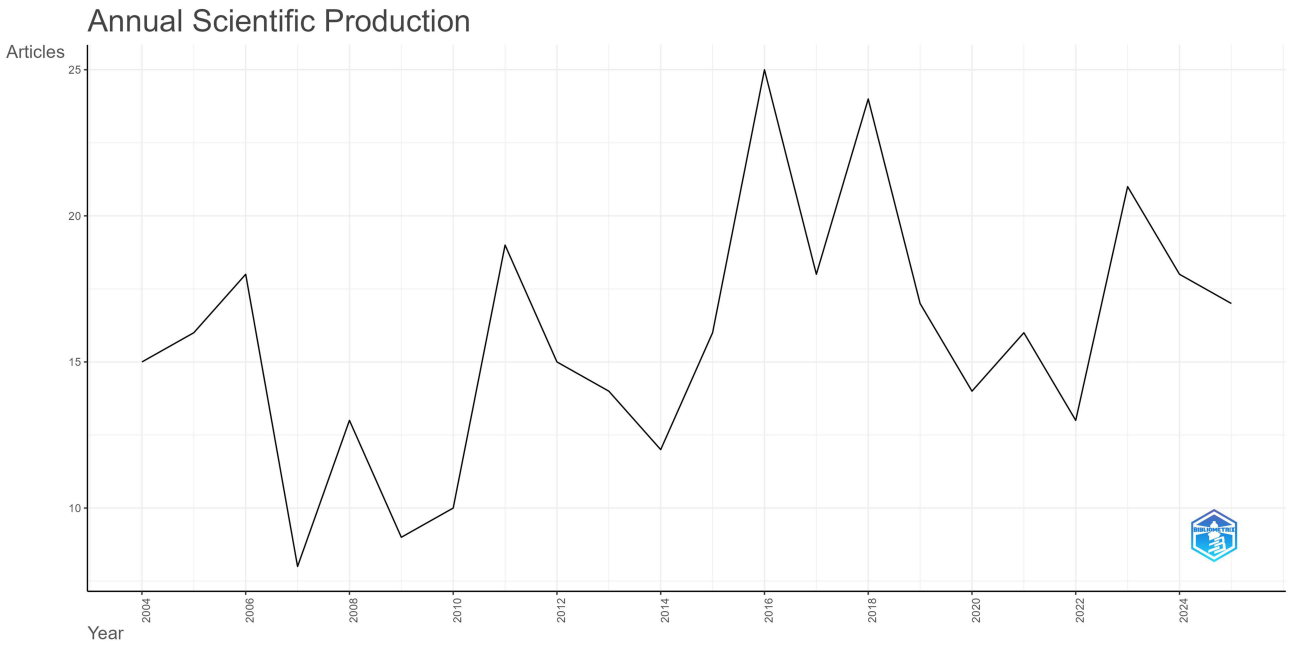

Figure 2 The annual number of publications.

publication in Spain, Australia, Canada, Germany, and Italy were considerably higher than those of other countries. Notably, Spain's average citation count exceeded 400, suggesting that research from these countries has attracted greater academic recognition within the field.

As illustrated in Figure 3B, the pink outer ring represents the citation performance of each country, further supporting this observation by visually indicating the relatively higher influence of studies from these regions.

At the institutional level, a total of 465 organisations were identified, among which 19 institutions contributed more than ten publications. Leading institutions such as Harvard University, Peking Union Medical College Hospital, and University College London demonstrated both high research productivity and extensive international collaboration. The institutional collaboration network generated using VOSviewer (Figure 4A) revealed a closely interconnected global research landscape in the field of COPD–GERD comorbidity. In the network visualisation, node size represents the number of publications from each institution, line thickness reflects the strength of collaboration, and node colour indicates the average year of publication. Overall, the network structure exhibited a distinct multicentric collaboration pattern with dense interconnections, suggesting a high degree of cooperation among research groups within this field.

Figure 4B illustrates the publication trends of major research institutions in the field of COPD–GERD comorbidity from 2004 to 2024. Between 2004 and 2010, only a few relevant studies were published, indicating that the topic had not yet received systematic attention. From 2010 to 2015, the number of publications began to increase markedly, with institutions such as Harvard University, Temple University, and the University of Michigan emerging as the earliest active contributors in this area. During 2016–2020, the annual publication output entered a relatively stable growth phase, with most institutions maintaining approximately ten papers each, suggesting that research in this field had become increasingly standardised and systematised. Since 2020, there has been a renewed surge in publication activity, particularly from Harvard University and Brigham and Women's Hospital, both of which have published more than 20 papers, marking a new period of research vitality. The current collaboration landscape of this field is characterised by a North America–Europe axis, with Asia gradually emerging as an important and rapidly developing contributor.

Journal and Author Analysis

As shown in Figure 5, the distribution of journals in the field of COPD-GERD comorbidity demonstrates a distinct pattern of concentration and stratification. From the perspective of publication trends (Figure 5A), the number of relevant

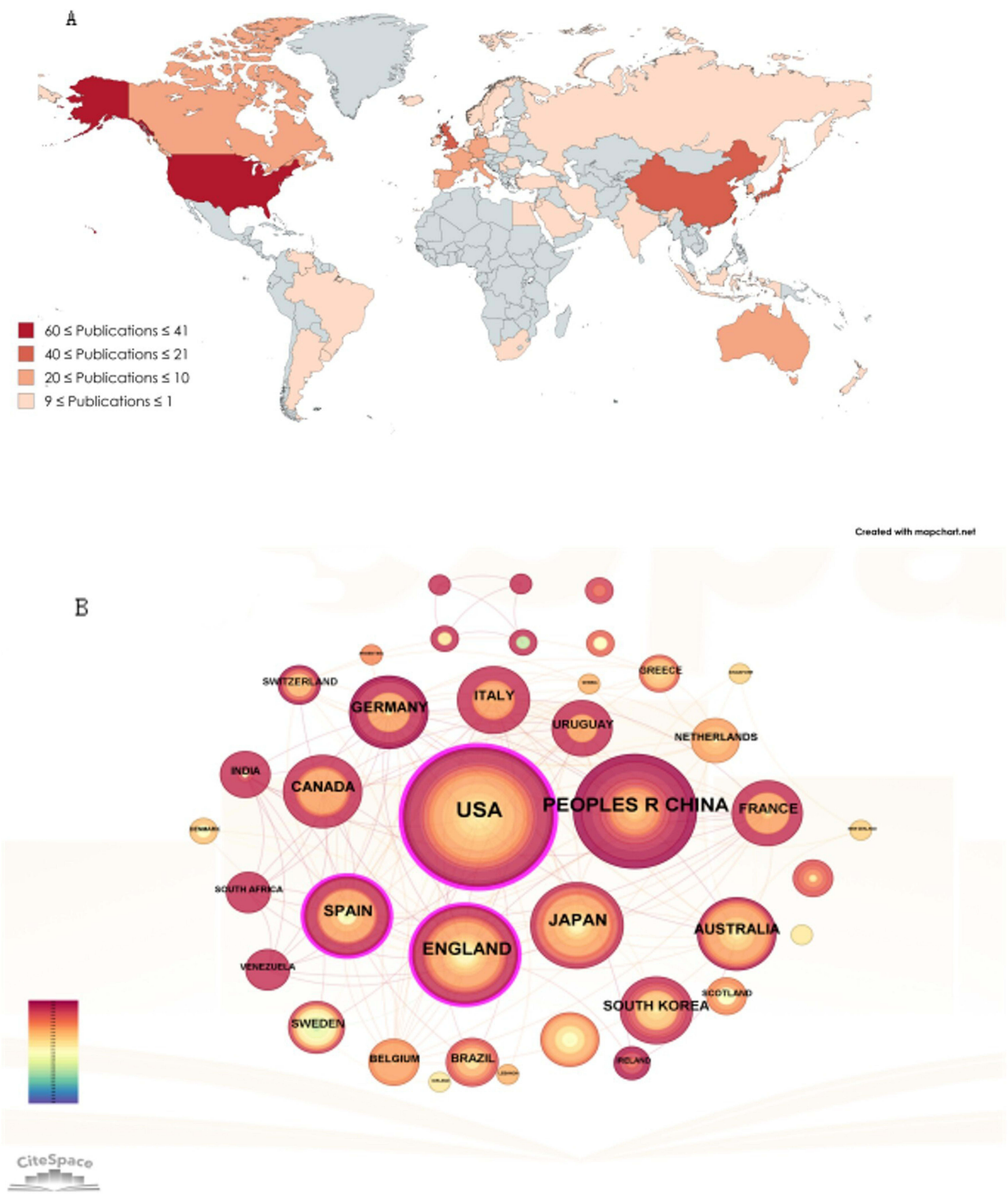

Figure 3 (**A**) Productions and distribution of countries; (**B**) National Cooperation Network.

studies has shown continuous growth since 2010, with a particularly rapid increase after 2015. In the early stage of research, studies were mainly published in general medical and gastroenterological journals, such as Alimentary Pharmacology & Therapeutics and BMC Pulmonary Medicine, reflecting scholars' initial exploratory interest in the role of gastro-oesophageal reflux in respiratory symptoms. As the research focus gradually shifted towards the

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Table 1 The Top 10 Countries by Number of Publications

Rank	Country	Documents	Citations	Average Citations	Total Link Strength
1	America	60	8389	139.82	116
2	China	39	3918	100.46	48
3	England	26	7780	299.23	105
4	Japan	22	4214	191.55	47
5	Spain	18	7305	405.83	100
6	Australia	13	3970	305.38	50
7	Canada	13	4834	371.85	93
8	Germany	13	4764	366.46	95
9	Italy	12	4766	397.17	91
10	South Korea	12	269	22.42	3

pathological mechanisms of chronic airway diseases and the multisystem interactions underlying comorbidities, publication platforms increasingly moved towards leading journals in the respiratory field. In recent years, journals such as the International Journal of Chronic Obstructive Pulmonary Disease (IJCOPD), American Journal of Respiratory and Critical Care Medicine (AJRCCM), Chest, Respiratory Medicine, and the European Respiratory Journal (ERJ) have become the primary outlets for research outputs. Among these, the IJCOPD has emerged as the core publication platform, characterised by a high volume of articles and serving as a major medium for academic communication in this domain.

Secondly, the journal impact analysis (Figure 5B) shows a clear hierarchical structure in the citation distribution of research outputs. The European Respiratory Journal, New England Journal of Medicine, and American Journal of Respiratory and Critical Care Medicine ranked as the top three most cited journals, with 2395, 2180, and 2131 citations respectively, reflecting strong academic influence and international recognition. Although the International Journal of Chronic Obstructive Pulmonary Disease (IJCOPD) had a lower total citation count (868) compared with these top-tier journals, its specialised focus and high concentration on COPD and comorbidity studies positioned it as a central platform within this research theme, with substantial influence within the discipline. Meanwhile, journals of moderate impact such as Chest, Respiratory Research, and Archivos de Bronconeumología have played important roles in disseminating clinical practice and regionally focused research, forming the intermediate tier of scholarly communication.

Finally, analysis of journal distribution based on Bradford's Law (Figure 5C) further confirmed the existence of a core cluster of journals in this field. The results indicated that IJCOPD, AJRCCM, Chest, Respiratory Medicine, and BMC Pulmonary Medicine constitute the core sources, which, despite being relatively few in number, collectively carry the majority of scholarly output in this domain. This distribution pattern suggests that research on COPD–GERD comorbidity has developed a relatively stable knowledge dissemination system, with publications predominantly concentrated in a small number of high-impact respiratory journals—characteristic of a mature disciplinary field.

As shown in Figure 6, research on COPD–GERD comorbidity has developed a relatively mature collaborative network structure. The author collaboration network (Figure 6A) indicates that research activities in this field are primarily driven by several core author groups, among which Martinez F.J., Criner G.J., Wedzicha J.A., Han M.K., Sin D.D., and Anzueto A. occupy central positions, demonstrating high levels of collaboration frequency and network connectivity. These authors maintain close research partnerships, and the overall network is densely structured, suggesting a notable degree of cohesion and stability in academic collaboration within the field. The publication distribution (Figure 6B) shows that Martinez F. J. had the highest number of publications (12 papers), followed by Criner G.J. and Wedzicha J.A. (each with 11 papers). Other highly productive authors, including Han M.K., Sin D.D., and Anzueto A., each published approximately nine papers. This pattern indicates that the major research outputs in this area are concentrated among a small group of scholars, reflecting a typical core-author structure. Further analysis of author impact (Figure 6C) revealed that Wedzicha J.A. had the highest local H-index (H = 11), while other key contributors, such as Anzueto A., Criner G.J., Martinez F.J., Celli B.R., and Sin D.D., each had an H-index of 9, demonstrating the high citation influence of their work within the field. Overall, research collaboration in the COPD–GERD comorbidity domain is dominated by a small number of core research groups.

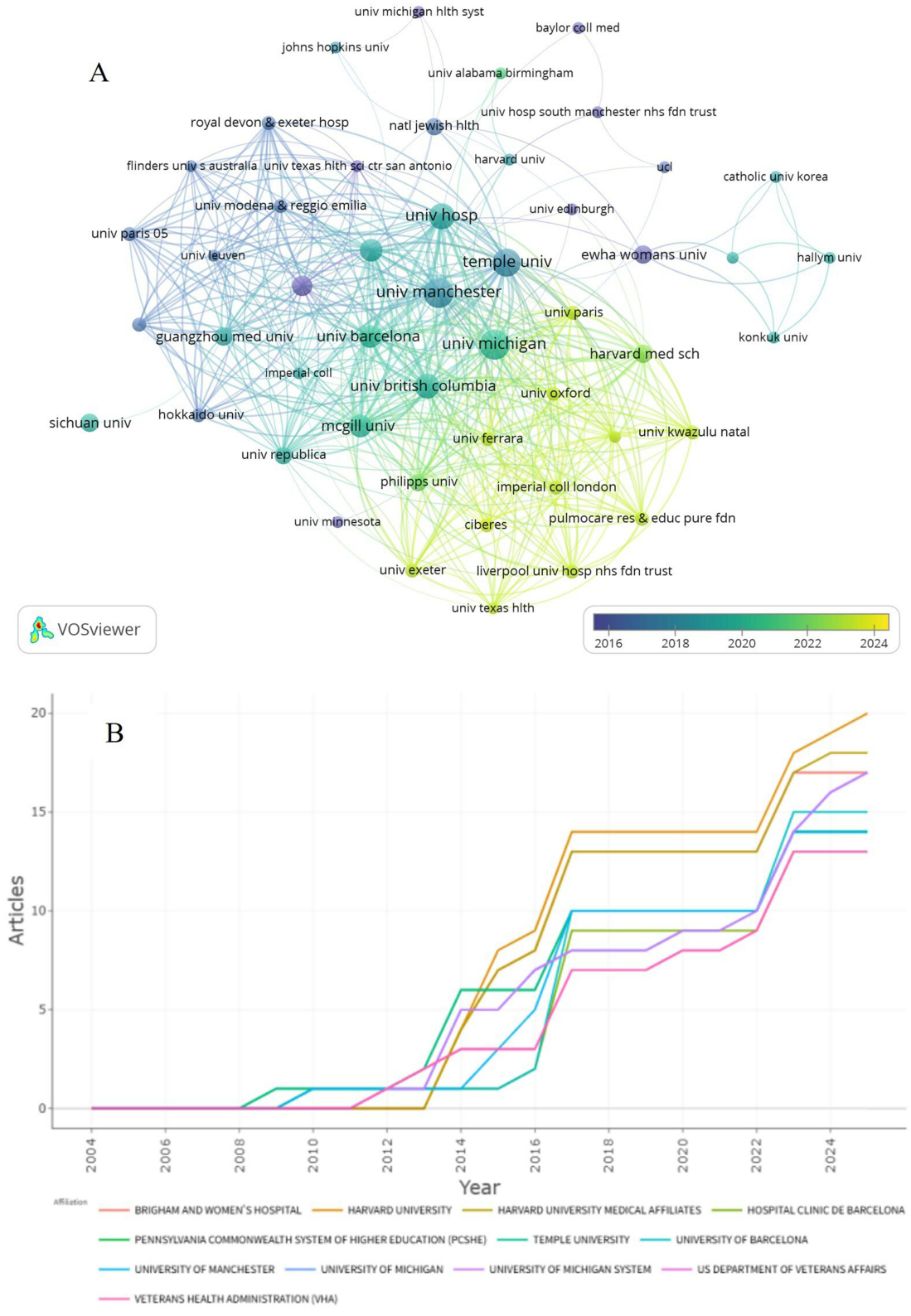

Figure 4 (**A**) Co-authorship of institutions; (**B**) Affiliations' Production over Time.

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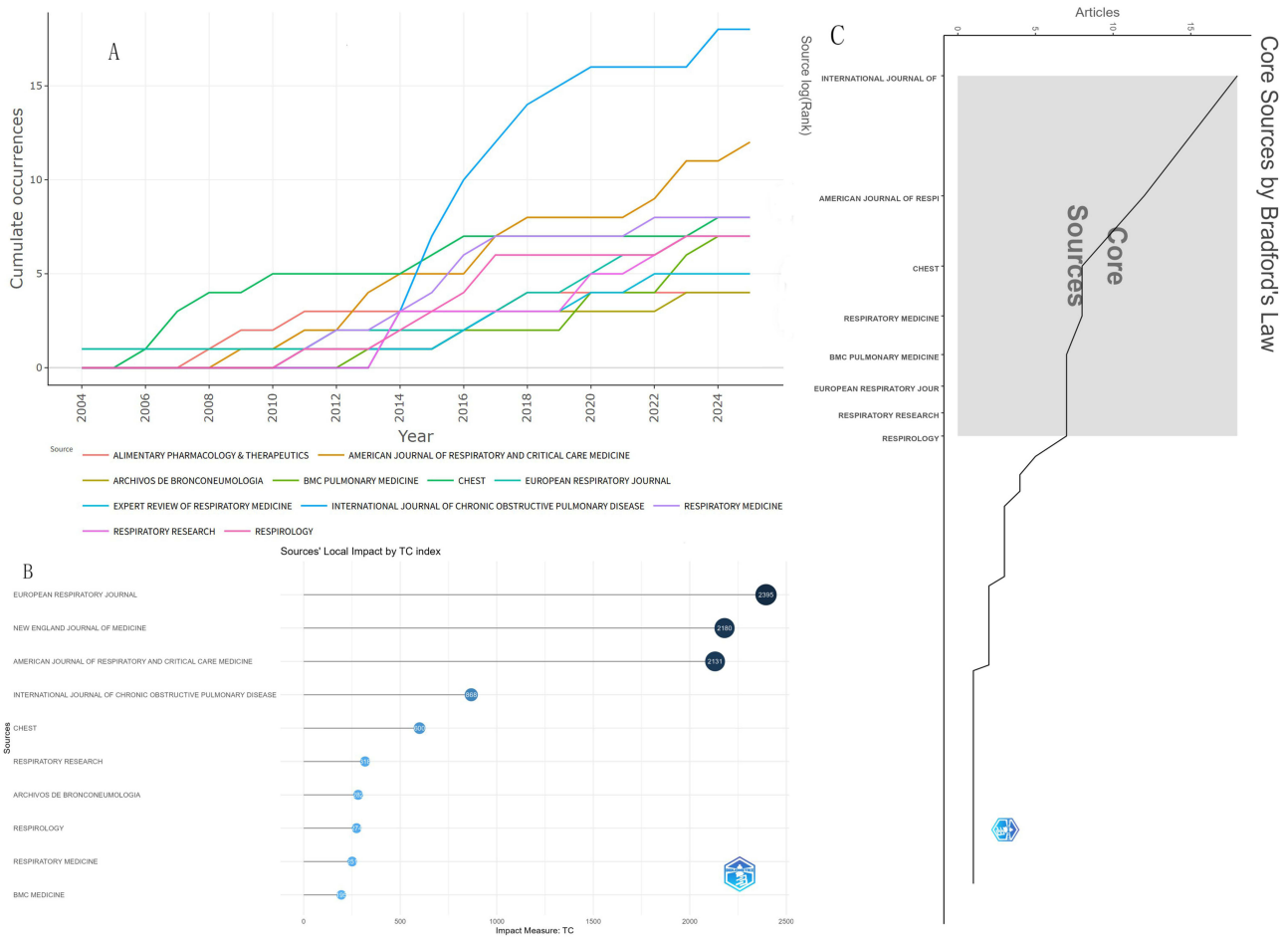

Figure 5 (**A**) Annual publication trends of the top 10 journals by number of articles; (**B**) Citation status of the top ten journals; (**C**) Core Sources by Bradford's Law.

The network structure is compact, and both scholarly output and influence are highly concentrated, reflecting the aggregative nature of international academic collaboration in this research area.

Highly Cited Publications and Co-Citation Network

The knowledge framework of COP-GERD comorbidity research was gradually established through clinical and epidemiological studies conducted between 2000 and 2015, and has been further expanded and refined over the past decade. The co-citation network (Figure 7A) revealed two major clusters of publications. The first, represented by Hurst JR, 2010, New England Journal of Medicine,[8] forms the green cluster, which focuses on the frequency, risk stratification, and prognosis of COPD exacerbations constituting a central research direction for understanding disease progression and the impact of comorbidities. The second, centred on Rascon-Aguilar IE, 2006, Chest[9] and Mokhlesi B, 2001, Chest,[10] forms the red cluster, which primarily explores the pathogenesis of GERD in patients with COPD and its effects on airway inflammation, pulmonary function, and quality of life. The close interconnection between these clusters indicates that COPD-GERD comorbidity research has evolved from isolated pathological descriptions to an integrated analysis of systemic pathophysiological mechanisms.

The results of local citation (LC) analysis, as presented in Table 2, further highlight the internal intellectual structure of this field. The most locally cited paper was Hurst JR, 2010, NEJM (LC = 69), whose proposed model of exacerbation frequency provided an important theoretical basis for subsequent studies on the effects of GERD during both stable and exacerbation phases of COPD. The second and third most locally cited papers Rascon-Aguilar IE, 2006, Chest (LC = 59) and Casanova C, 2004, Eur Respir J[11] (LC = 56) investigated the high prevalence of GERD in COPD patients and its

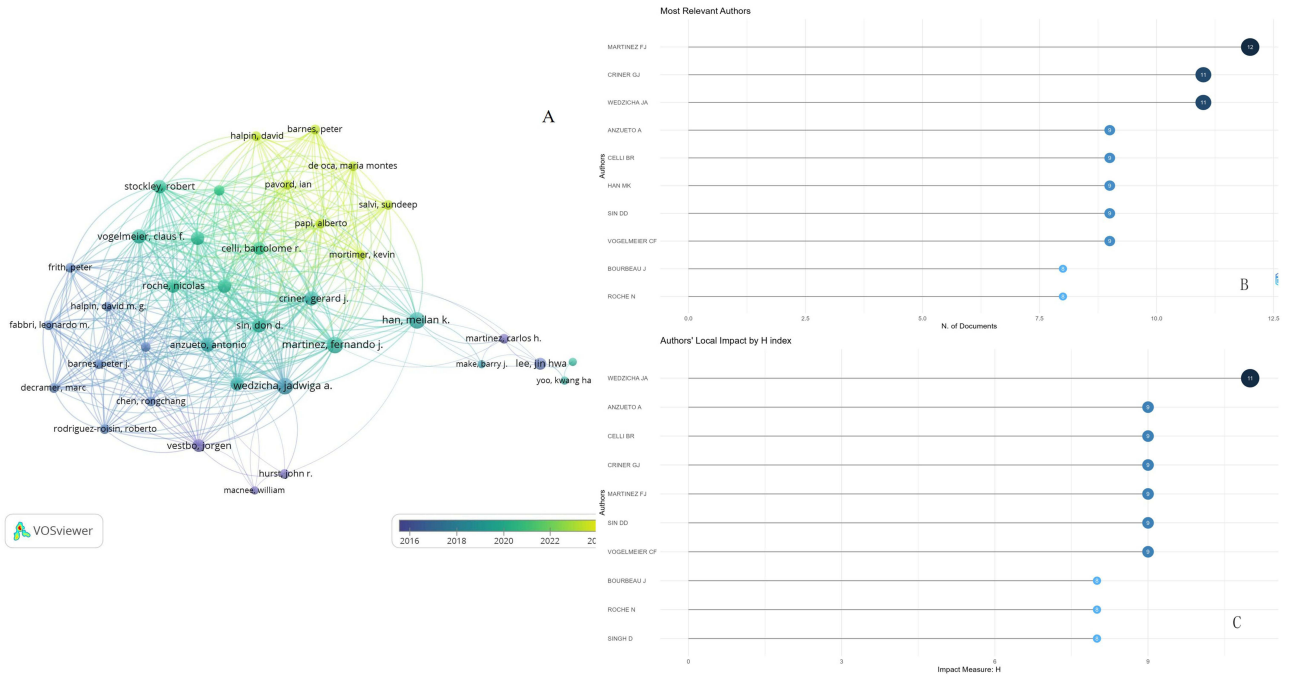

Figure 6 (**A**) A Co-authorship of authors; (**B**) Top 10 authors by number of posts; (**C**) Top 10 authors by citation count.

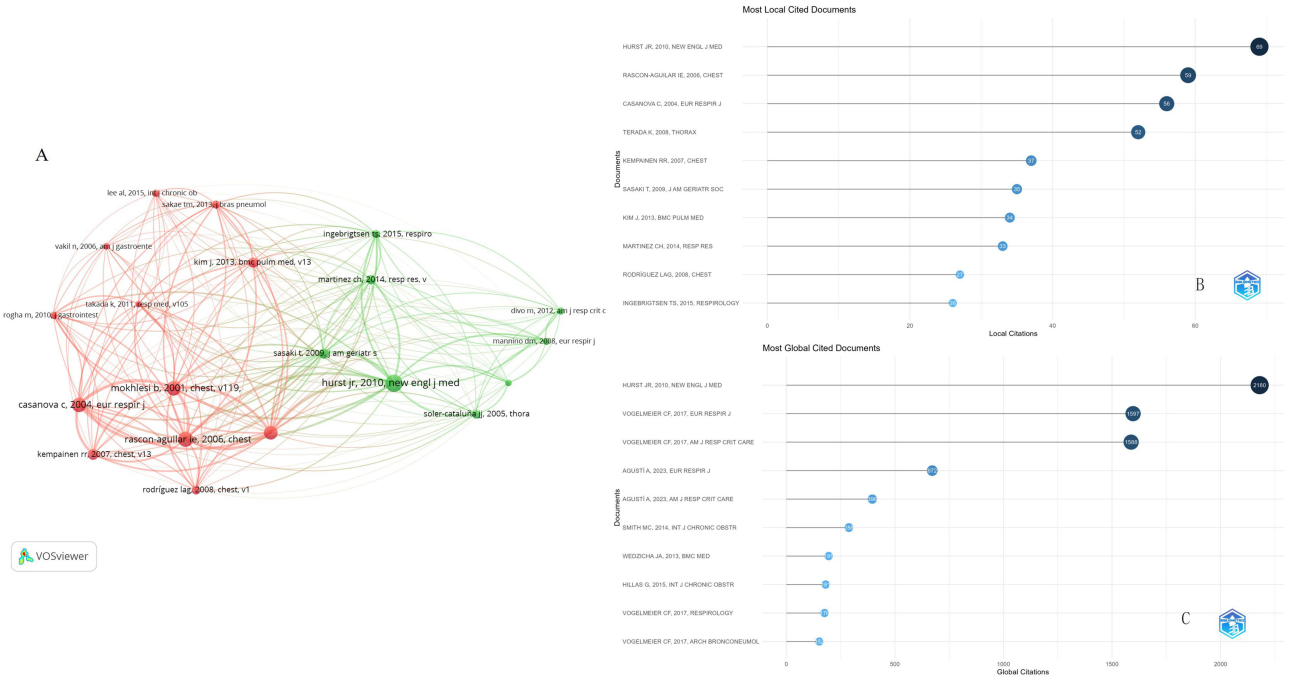

Figure 7 (**A**) Co-citation network of cited references related to COPD and GERD comorbidity; (**B**) Top 10 most locally cited documents in the COPD–GERD comorbidity dataset; (**C**) Top 10 most globally cited documents in the COP.

aggravating effects on clinical symptoms, providing key epidemiological evidence for the comorbidity relationship. Several other papers (eg, Kempainen RR, 2007; Martinez CH, 2014; Ingebrigtsen TS, 2015) had relatively lower global citation counts but exhibited high LC/GC ratios (>50%), suggesting strong field-specific relevance and local influence. These studies represent the internal intellectual core of this research domain (Figure 7B).

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Table 2 The Top 10 Publications By Local Citations

Rank	Document	DOI	Year	Local Citations	Global Citations	LC/GC Ratio (%)
1	Hurst JR, 2010, New Engl J Med	10.1056/NEJMoa0909883	2010	69	2180	3.17
2	Rascon-Aguilar IE, 2006, Chest	10.1378/chest.130.4.1096	2006	59	127	46.46
3	Casanova C, 2004, Eur Respir J	10.1183/09031936.04.00107004	2004	56	125	44.80
4	Terada K, 2008, Thorax	10.1136/thx.2007.092858	2008	52	141	36.88
5	Kempainen RR, 2007, Chest	10.1378/chest.06-2264	2007	37	74	50.00
6	Sasaki T, 2009, J Am Geriatr Soc	10.1111/j.1532–5415.2009.02349.x	2009	35	72	48.61
7	Kim J, 2013, BMC Pulm Med	10.1186/1471-2466-13-51	2013	34	89	38.20
8	Martinez CH, 2014, Resp Res	10.1186/1465-9921-15-62	2014	33	58	56.90
9	Rodríguez LAG, 2008, Chest	10.1378/chest.08-0902	2008	27	56	48.21
10	Ingebrigtsen TS, 2015, Respirology	10.1111/resp.12420	2015	26	50	52.00

Table 3 The Top 10 Publications By Global Citations

Rank	Document	DOI	Year	Total Citations	TC per Year
1	Hurst JR, 2010, New Engl J Med	10.1056/NEJMoa0909883	2010	2180	136.25
2	Vogelmeier CF, 2017, Eur Respir J	10.1183/13993003.00214–2017	2017	1597	177.44
3	Vogelmeier CF, 2017, Am J Resp Crit Care	10.1164/rccm.201701–0218PP	2017	1588	176.44
4	Agustí A, 2023, Eur Respir J	10.1183/13993003.00239-2023	2023	672	224.00
5	Agustí A, 2023, Am J Resp Crit Care	10.1164/rccm.202301–0106PP	2023	396	132.00
6	Smith MC, 2014, Int J Chronic Obstr	10.2147/chronic obstructive pulmonary disease.S49621	2014	288	24.00
7	Wedzicha JA, 2013, BMC Med	10.1186/1741-7015-11-181	2013	195	15.00
8	Hillas G, 2015, Int J Chronic Obstr	10.2147/chronic obstructive pulmonary disease.S54473	2015	181	16.45
9	Vogelmeier CF, 2017, Respirology	10.1111/resp.13012	2017	176	19.56
10	Vogelmeier CF, 2017, Arch Bronconeumol	10.1016/j.arbres.2017.02.001	2017	152	16.89

The global citation (GC) results summarised in Table 3 illustrate the broader international influence of these publications. Hurst JR, 2010, NEJM received a total of 2180 global citations, demonstrating that its findings not only serve as a cornerstone of COPD–GERD comorbidity research but are also widely referenced in the broader fields of COPD risk assessment and disease management. Vogelmeier CF, 2017 published two highly influential papers in the Eur Respir J and Am J Respir Crit Care Med with 1597 and 1588 citations, respectively. These GOLD guideline updates established a standardised framework for COPD diagnosis and treatment, thereby providing a unified clinical reference for comorbidity research. More recent publications by Agustí A, 2023 (GC = 672 and 396) have rapidly accumulated citations, indicating that academic attention has shifted towards multisystem comorbidities, metabolic mechanisms, and precision medicine. This temporal evolution reflects a knowledge transition from clinical observation to systemic mechanisms and integrated management (Figure 7C).

In summary, locally cited publications reflect the internal academic accumulation and foundational knowledge within the COPD-GERD comorbidity domain, while globally cited papers demonstrate the connection of this research theme to the mainstream directions of international respiratory medicine. Hurst JR, 2010 ranked highest in both local and global citation analyses, indicating its cross-level academic influence and identifying it as a bridging paper within the field. In contrast, papers such as Rascon-Aguilar IE, 2006 and Casanova C, 2004 were more prominent in local citation analysis, underscoring their central role within the thematic domain, yet their influence in broader respiratory research remained relatively limited—reflecting a distinct pattern of field-specific citation.

Keyword Co-Occurrence and Thematic Evolution

As shown in Figure 8, research hotspots in the field of COPD-GERD comorbidity are primarily concentrated around chronic obstructive pulmonary disease, gastro-oesophageal reflux disease, comorbidity, and their associated clinical outcomes. The

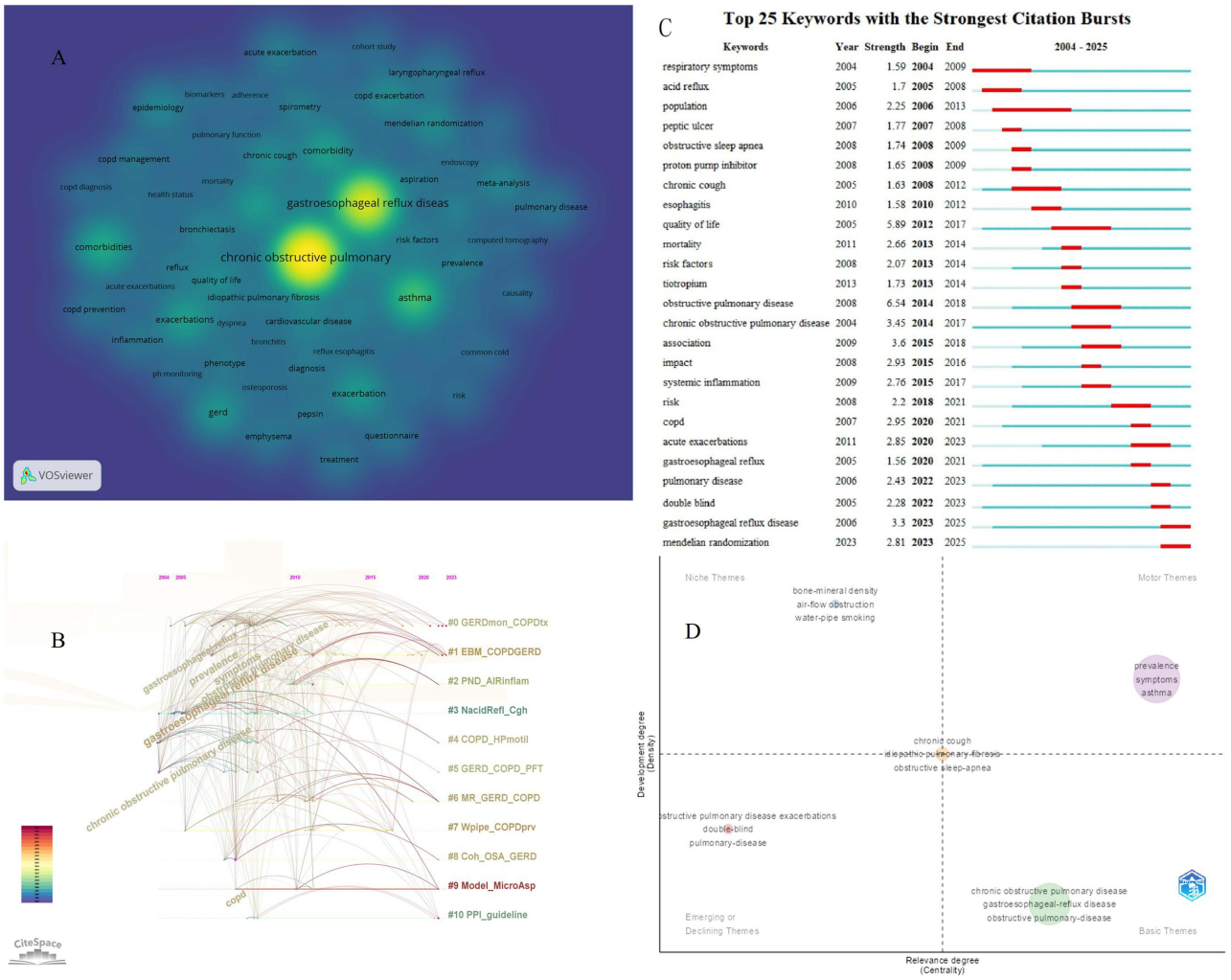

Figure 8 (**A**) Keyword density visualization map generated by VOS viewer; (**B**) Timeline view of keyword clusters generated by CiteSpace; (**C**) Top 25 keywords with the strongest citation bursts; (**D**) Document coupling.

keyword density visualisation map (Figure 8A) indicates that terms such as gastro-oesophageal reflux disease, chronic obstructive pulmonary disease, comorbidity, exacerbation, and quality of life exhibit the highest co-occurrence frequencies. This suggests that current research mainly focuses on the prevalence and pathophysiological mechanisms of GERD among COPD patients, as well as its effects on disease exacerbation, symptom control, and quality of life. Additionally, the appearance of secondary keywords such as asthma, bronchiectasis, and systemic inflammation indicates that the research field is gradually expanding towards multisystem inflammation and interactions among comorbidities.

The CiteSpace keyword clustering timeline (Figure 8B) further reveals the evolutionary trajectory of research themes in this field. From a temporal perspective, early studies between 2004 and 2010 mainly focused on topics related to respiratory symptoms such as respiratory function, aspiration, and chronic cough emphasising the influence of GERD on airway reactivity and pulmonary function. Between 2010 and 2020, research themes expanded to include keywords such as fundoplication, pepsin, and lung disease, reflecting the growing interest in surgical interventions and pathobiochemical mechanisms. Since 2020, emerging hotspots have included proton pump inhibitor, microaspiration, and Mendelian randomisation, suggesting that research in this field is transitioning from clinical observation towards molecular mechanism exploration and causal inference analysis, highlighting the application of precision medicine approaches in comorbidity research.

The keyword burst analysis (Figure 8C) further validates this evolutionary pattern. During 2004–2010, burst terms such as respiratory symptoms, acid reflux, and obstructive sleep apnoea primarily reflected clinical manifestations and pathophysiological studies. Between 2011 and 2017, keywords with strong burst intensities such as quality of life, mortality, and systemic inflammation indicated a shift in focus towards the impact of comorbidities on survival outcomes and inflammatory responses. Since 2018, acute exacerbations, gastro-oesophageal reflux, and Mendelian randomisation have emerged as the most prominent burst terms, suggesting that researchers have increasingly adopted genetic epidemiology and causal inference methodologies to explore the underlying biological links between GERD and COPD. This demonstrates that the research paradigm has advanced from clinical correlation validation to mechanistic and predictive investigation.

The bibliographic coupling clustering analysis (Figure 8D) further elucidated the thematic structure and research priorities at the document level. The clustering results identified three major thematic categories:

(1) The "chronic obstructive pulmonary disease-gastro-oesophageal reflux disease" cluster, representing the core direction of the field, focusing on the interaction and mechanistic studies of the two diseases;

(2) The "comorbidities-asthma" cluster, emphasising the comorbid characteristics and systemic inflammatory connections among respiratory disorders; and

(3) The "disease management-prevention" cluster, corresponding to emerging research directions in intervention and prevention, such as PPI therapy, combined inhalation management, and risk stratification models. Within the overall structure, the COPD-GERD cluster displayed the highest centrality and influence, indicating its dominance within the knowledge network and its role as the core theme of this field.

Collectively, the four analytical approaches corroborate one another, demonstrating that research on COPD-GERD comorbidity has evolved from "symptom and epidemiological association", to "pathophysiological mechanisms and intervention strategies", and finally to "systemic mechanisms and precision medicine". Early research mainly focused on clinical observation and patient outcomes; mid-stage studies increasingly addressed inflammatory responses and mechanistic pathways; and recent investigations have shown a trend towards multidisciplinary integration and methodological innovation. The current research hotspots have shifted from traditional epidemiological statistics to the integration of genomics, immunology, and bioinformatics, indicating that this field is undergoing a critical transition from empirical investigation to mechanistic and predictive research.

Discussion

Global Research Landscape and Multidisciplinary Features

Through bibliometric and visualisation analyses, this study revealed the international research landscape of COPD-GERD comorbidity and further explored the relationship between the two conditions from both clinical and mechanistic perspectives. The findings demonstrate that over the past two decades, this field has undergone significant academic expansion, particularly forming relatively stable interdisciplinary collaboration networks across Europe and North America. Research institutions in North America and Europe such as Harvard University, University of Michigan, University of Manchester, and Imperial College London—have played dominant roles in both publication output and academic influence. Scholars from these institutions have not only focused on the epidemiological characteristics and exacerbation mechanisms of COPD but have also actively investigated the role of gastro-oesophageal reflux in respiratory diseases, thereby promoting disciplinary integration between the digestive and respiratory sciences.[12,13] In recent years, research institutions in Asia have demonstrated a rapid increase in publication volume, although their overall network centrality remains relatively low. This indicates that future progress will benefit from enhanced multicentre and cross-regional collaborations to facilitate data sharing and standardised research design. Such a trend towards multidisciplinary cooperation reflects the complexity of COPD-GERD comorbidity, as investigations have moved beyond a single-system focus into the broader respiratory–digestive–immune interface.

Bidirectional Pathophysiological Mechanisms Between COPD and GERD

To further summarize the pathophysiological mechanisms of comorbidity between COPD and GERD, we conducted a brief review and synthesis based on the included literature. The core issue in COPD–GERD comorbidity lies in their bidirectional pathophysiological mechanisms. On one hand, GERD can directly injure the lower airway epithelium through acid reflux and microaspiration, inducing inflammation and bronchial hyperreactivity.[8,9] Several studies have reported the presence of both overt and silent reflux in COPD patients, with the frequency of reflux positively correlated with the number of acute exacerbations.[14,15] During aspiration, pepsin and bile acids can activate the NF-κB signalling pathway in airway epithelial cells, increasing the release of IL-6 and TNF-α, thereby establishing a sustained inflammatory microenvironment.[16,17]

On the other hand, respiratory mechanical abnormalities caused by COPD such as diaphragmatic flattening and fluctuations in intrathoracic pressure along with the relaxation of the lower oesophageal sphincter induced by inhaled bronchodilators, can in turn exacerbate reflux symptoms.[18] This composite mechanism, involving mechanical, inflammatory, and neuro-reflex components, forms a vicious cycle between the two diseases.

Moreover, the oesophago-bronchial reflex provides evidence for a non-aspiration-mediated pathological pathway. When refluxate stimulates the oesophageal mucosa, vagal afferent signalling can trigger bronchoconstriction and the cough reflex, leading to increased airway resistance during the night.[19,20] This mechanism explains why many COPD patients experience nocturnal cough and dyspnoea even in the absence of overt GERD symptoms. Together, these pathophysiological mechanisms illustrate the reciprocal relationship between COPD and GERD whereby COPD-induced intrathoracic pressure changes and airflow limitation increase the risk of reflux, while GERD-associated airway inflammation and reflex bronchoconstriction further aggravate respiratory dysfunction.

Systemic Inflammation and Metabolic Correlation

An increasing body of evidence suggests that the comorbidity between COPD and GERD is not merely a consequence of localised organ dysfunction, but rather a manifestation of systemic inflammation and metabolic imbalance. The chronic inflammatory state associated with COPD and the oxidative stress induced by GERD share overlapping molecular pathways, including the NF-κB, IL-1β, and TGF-β signalling axes. This systemic inflammation can result in endothelial dysfunction and smooth muscle remodelling, thereby worsening airway obstruction.[21,22] In addition, GERD patients frequently present with metabolic syndrome and obesity, both of which are strongly associated with increased diaphragmatic load and elevated oesophageal pressure representing important shared risk factors for the comorbidity of GERD and COPD.[23,24] Moreover, the gut-lung axis has recently emerged as a novel area of research interest. Reflux-related acid exposure and gastrointestinal dysbiosis may influence pulmonary immune responses through circulatory or vagal pathways, thereby promoting the propagation of inflammation.[25,26] Studies have shown that GERD patients exhibit reduced gut microbiota diversity accompanied by disturbances in short-chain fatty acid metabolism, changes that may contribute to the persistence of chronic inflammation in COPD.[27–29] Collectively, these findings suggest that the biological basis of COPD-GERD comorbidity may be driven by systemic inflammatory and metabolic dysregulation, rather than by the local reflux effect alone.

Clinical Outcomes and Complexity of Intervention Strategies

At the clinical level, the comorbidity of COPD and GERD has a significant impact on disease progression and prognosis. Studies have shown that COPD patients with concomitant GERD experience higher frequencies of acute exacerbations and markedly reduced quality of life. Furthermore, the presence of GERD is closely associated with chronic cough, airway hyperreactivity, and sleep-related breathing disorders, symptoms that are often misattributed to COPD progression, thereby increasing the complexity of clinical diagnosis and management.

In terms of treatment strategies, proton pump inhibitors (PPIs) remain the principal pharmacological intervention. PPIs effectively alleviate GERD symptoms and, according to several studies, may reduce the frequency of COPD exacerbations.[30] However, long-term PPI use can lead to reduced gastrointestinal acidity, which impairs the absorption of essential minerals such as magnesium. Low magnesium levels are associated with impaired muscle function.[31] Moreover, prolonged PPI therapy may alter the gut microbiota composition, thereby increasing infection risk[32] an issue that has

gained attention in recent studies. Additionally, some evidence suggests that H_2-receptor antagonists may be superior to PPIs in reducing microaspiration, though clinical data remain limited.[33]

The integrated care model has been proposed as a promising future direction, encompassing respiratory rehabilitation, weight management, dietary modification, and pharmacological optimisation as multidimensional intervention strategies.[34,35] Such interventions may simultaneously alleviate COPD symptoms and GERD reflux by improving respiratory muscle function and reducing abdominal pressure fluctuations. Future research should prioritise prospective randomised controlled trials to validate the long-term prognostic benefits of integrated management in COPD-GERD comorbidity.

Genetic Susceptibility and Precision Medicine Direction

In recent years, studies in genetic and molecular epidemiology have provided new interpretative frameworks for understanding the comorbidity between COPD and GERD. Genomic analyses have identified overlapping genetic loci involved in the regulation of airway inflammation and oesophageal motility, suggesting potential shared genetic mechanisms underlying both conditions.[36] Mendelian randomisation studies have further revealed that genetic susceptibility to GERD may increase the risk of developing COPD, while the reverse association has not yet been clearly established.[37,38]

Moreover, gene–environment interaction models indicate that smoking, obesity, and dietary factors may enhance the expression of these susceptibility genes through epigenetic mechanisms.[39,40] This suggests that the development of COPD-GERD comorbidity has a genetic basis, yet its clinical manifestation is significantly modulated by environmental factors.

Future research should integrate multi-omics data with artificial intelligence–driven models to explore precision phenotyping and individualised intervention strategies, thereby facilitating a paradigm shift from statistical correlation to biological causation in COPD-GERD comorbidity research.

Potential Role of Traditional and Complementary Medicine

Traditional and Complementary Medicine offers new perspectives for the integrated management of COPD-GERD comorbidity.

According to traditional Chinese medicine (TCM) theory, the "lung and stomach are interconnected", implying that dysfunctions of the respiratory and digestive systems may influence each other reciprocally-an idea that resonates with modern concepts of the "gut-lung axis" and systemic inflammation.[41,42] Studies have demonstrated that Chinese herbal formulations and bioactive compounds, such as baicalin and glycyrrhizic acid, can inhibit the NF-κB pathway, reduce IL-6 and TNF-α levels, thereby attenuating airway inflammation and improving respiratory function.[43,44]

In relation to GERD, acupuncture and herbal extracts such as curcumin and flavonoids have been shown to increase lower oesophageal sphincter pressure, inhibit gastric acid secretion, and reduce inflammatory responses, which may also be beneficial for reflux-related respiratory symptoms.[45,46] These interventions possess multi-target and dual-system regulatory potential, suggesting possible synergistic effects in the prevention and management of respiratory-digestive comorbidities. However, the current evidence is largely derived from small-sample studies, and further high-quality randomised controlled trials are required to validate their efficacy and safety. Future research should seek to integrate traditional medical concepts with modern biological methodologies, exploring the potential role of TCM in the precision management of multisystem comorbidities.

Future Perspectives

In summary, the development of COPD-GERD comorbidity results from the interaction of multiple factors, including anatomical structure, neural regulation, and inflammatory responses. Research priorities are shifting from single-system observations towards multidimensional mechanistic integration, reflecting a pronounced trend of disciplinary convergence and technological fusion. Future studies should deepen along the following directions:

(1) Multicentre longitudinal studies: Establish unified diagnostic criteria and reflux monitoring systems to quantitatively evaluate the long-term prognostic impact of comorbidity on COPD. Mechanistic exploration: Focus on the roles of pepsin, bile acids, and oxidative stress pathways in airway inflammation.(2) Multi-omics integration: Combine genomic, epigenetic, and microbiome data to elucidate the regulatory mechanisms of the "gut-lung-oesophagus" axis.(3) Precision intervention: Develop individualised therapeutic strategies based on genetic susceptibility and inflammatory phenotyping.

(4) Integrated management models: Construct multidisciplinary collaborative frameworks encompassing respiratory rehabilitation, digestive function modulation, and psychological support.

Through these approaches, research on COPD-GERD comorbidity may achieve a comprehensive translational continuum from statistical association to pathophysiological mechanism, and ultimately to clinical application—thereby providing new theoretical foundations and practical guidance for the integrated prevention and management of chronic respiratory diseases.

Limitations

This study systematically elucidated the research landscape of COPD–GERD comorbidity using bibliometric methods; however, several limitations should be acknowledged. First, the data source was primarily limited to the Web of Science database, which may have resulted in the omission of relevant publications indexed elsewhere. Second, citation counts are inherently time-dependent—earlier studies may be overrepresented, whereas recent high-quality publications might not yet have fully reflected their academic impact. Third, the clustering results generated by VOSviewer and CiteSpace are based on keyword co-occurrence, which may not fully capture semantic context, leading to potential algorithmic bias. In addition, the study did not incorporate weighted analyses of publication quality or collaboration intensity, which could underestimate the contributions of emerging research groups. Finally, although the present study extended its discussion by integrating mechanistic evidence, bibliometric data alone cannot directly verify pathophysiological processes. Therefore, prospective clinical and experimental studies remain essential to substantiate the findings and validate causal mechanisms.

Conclusions

This study demonstrates that research on COPD-GERD comorbidity is undergoing a paradigm shift from epidemiological observation towards mechanistic exploration and precision management. Global research hotspots are concentrated on reflux-related inflammation, non-acid reflux, microaspiration, and systemic inflammatory pathways. In recent years, genetic and multi-omics studies have further advanced understanding of the biological mechanisms underlying the association between the two diseases.

The United States and Europe remain the leading contributors in terms of research output and academic influence, while Asian countries have shown rapidly increasing scientific activity. Mechanistically, GERD aggravates COPD through reflux injury, the oesophago–bronchial reflex, and systemic inflammatory responses, whereas the respiratory mechanical abnormalities associated with COPD promote reflux formation in turn.

Clinically, PPIs provide limited therapeutic benefit, and their long-term safety requires further evaluation. Integrated management and individualised intervention are expected to represent the future direction of treatment.

Overall, this study provides quantitative insights into the evolutionary trajectory and scientific foundation of COPD-GERD comorbidity research and offers a conceptual framework for developing interdisciplinary prevention and management strategies.

Disclosure

The authors report no conflicts of interest in this work.

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