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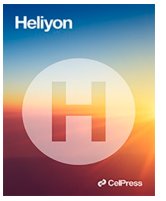

Research article

Research trends on airway remodeling: A bibliometrics analysis

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ABSTRACT

Background: Airway remodeling is an essential pathological basis of respiratory diseases such as asthma and COPD, which is significantly related to pulmonary function and clinical symptoms. And pulmonary disease can be improved by regulating airway remodeling. This study aimed to establish a knowledge map of airway remodeling to clarify current research hotspots and future research trends.

Methods: A comprehensive search was performed to analyze all relevant articles on airway remodeling using the Web of Science Core Collection Database from January 01, 2004 to June 03, 2023.2 reviewers screened the retrieved literature. Besides, the CiteSpace (6.2. R3) and VOSviewer (1.6.19) were utilized to visualize the research focus and trend regarding the effect of airway remodeling.

Results: A total of 4077 articles about airway remodeling were retrieved. The United States is the country with the most published literature, underscoring the country's role in airway remodeling. In recent years, China has been the country with the fastest growth in the number of published literature, suggesting that China will play a more critical role in airway remodeling in the future. From the perspective of co-operation among countries, European co-operation was closer than Asian co-operation. The co-citation analysis showed that 98,313 citations were recorded in 3594 articles, and 25 clusters could be realized. In recent years, Burst detection shows that oxidative stress and epithelial-mesenchymal transition are hot words.

Conclusions: Based on the bibliometric analysis of airway remodeling studies in the past 20 years, a multi-level knowledge structure map was drawn, it mainly includes countries, institutions, research fields, authors, journals, keywords and so on. The research directions represented by obstructive airway disease, PDGF-BB treatment of airway smooth muscle, allergen-induced airway remodeling, extracellular matrix, and non-coding RNA are the research hotspots in the field of airway remodeling. While the risk factors for airway remodeling, the application of new noninvasively assessing tools, biomarkers as well as The molecular mechanism represented by EMT and autophagy had been frontiers in recent years.

1. Introduction

Airway remodeling refers to structural and functional changes in airway tissue due to repeated chronic inflammatory stimuli and

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incomplete repair [1]. The pathological changes include goblet cell metaplasia, extracellular matrix protein deposition and fibrosis, overexpression of angiogenic factors, and proliferation and/or hypertrophy of airway smooth muscle cells [2]. Airway remodeling is more common in pulmonary diseases such as asthma, COPD, bronchiectasis and cystic fibrosis, which is one of the most challenging problems in these diseases and is also a significant cause of irreversible airway stenosis and airflow limitation [3]. The crucial role that resident cells play in the pathological progression of airway remodeling is becoming increasingly recognized. These cells, which include fibroblasts, macrophages, neutrophils, lymphocytes, mast cells, and Innate Lymphoid Cells (ILC), contribute to airway remodeling through the direct or indirect release of pivotal factors such as cytokines, proteases, and growth factors [4–6]. Despite these findings, the specific role of lung-resident cells in airway remodeling remains shrouded in uncertainty. This area thus merits further attention in future clinical and basic research, particularly with an emphasis on targeting specific types of cells and/or remodeling factors [7]. Notwithstanding the progress made thus far, we are yet to identify a reliable biomarker for airway remodeling. Furthermore, non-invasive imaging technology that allows for the direct observation of airway remodeling is still in the developmental phase. Therefore, it presents another significant area of research focus moving forward. In conclusion, evaluating the current state of knowledge and projecting future trends in airway remodeling bear considerable clinical significance. Our understanding of this field will undoubtedly have far-reaching effects on diagnostic and therapeutic strategies for diseases involving the airways.

Bibliometric analysis is a method to study the characteristics and development trends of literature [8]. It comprehensively evaluates and analyzes the number, author, institution, citation and other dimensions of literature, so as to understand the development status and trend of specific fields and provide support for academic research and discipline construction [9]. This study used bibliometric methods to analyze the overall status quo and possible future trends in airway remodeling.

2. Data and methods

2.1. Data sources and search strategy

A literature search from January 01, 2004 to June 03, 2023 was performed using the Web of Science Core Collection Database. WOS Core Collection is the most powerful and authoritative search engine for research literature that comprehensively covers key research outputs worldwide [10]. Two reviewers screened abstracts retrieved and potentially eligible articles during the literature search. Any discrepancies between reviewers regarding study selection were resolved by consulting a third reviewer. The search terms included: TS= (“Airway remodeling" OR “Airway remodeling" OR “airway wall remodeling" OR “airway wall remodeling"). The search indices included Science Citation Index Expanded (SCI-Expanded), Social Sciences Citation Index (SSCI), Arts Humanities Citation Index (AHCI), Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH), Conference Proceedings Citation Index-Science (CPCI–S), Book Citation Index Science (BKCI–S), Emerging Sources Citation Index (ESCI) and Book Citation Index -Social Sciences Humanities (BKCI-SSH). We limited our search to literature written in English and limited the literature type to review

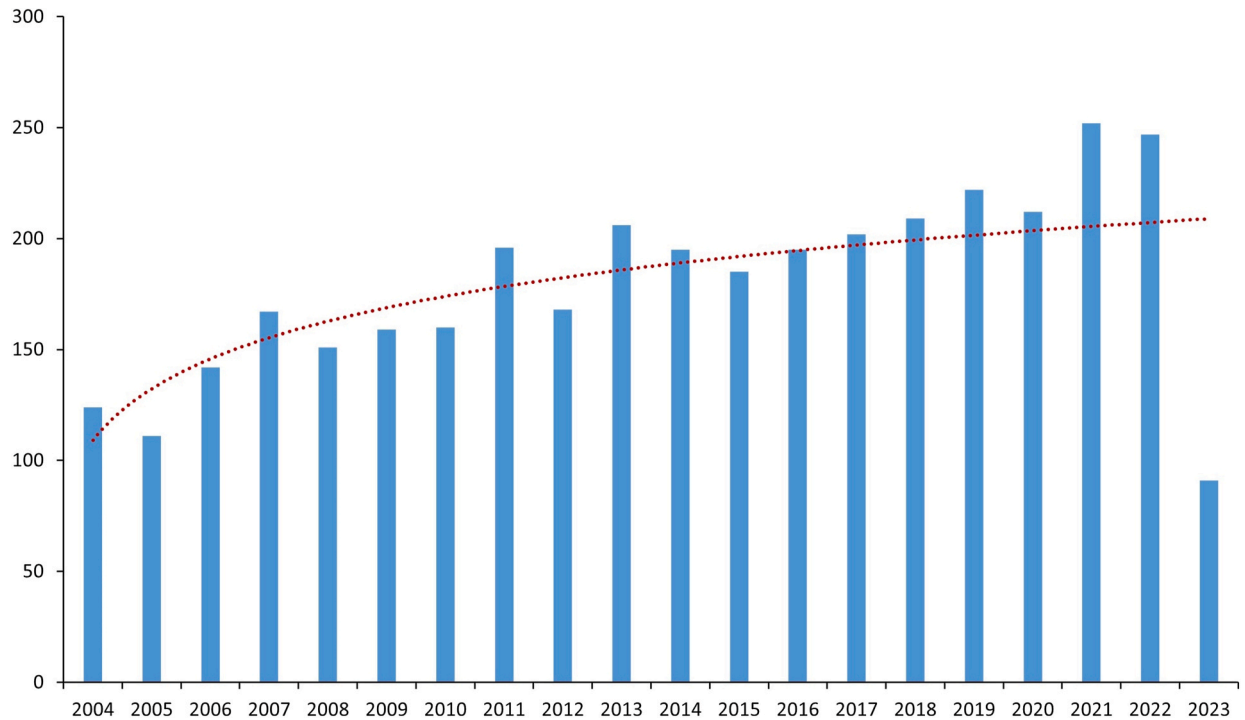

Fig. 1. The statistics of airway remodeling-related articles from 2004 to 2023.

and article.

2.2. Literature quantity

A total of 4077 references were identified from January 1, 2004 to June 3, 2023. After excluding ineligible and duplicate articles, 4077 articles and reviews related to airway remodeling were identified.

2.3. Visualization and statistical analyses

CiteSpace 6.2. R3 and VOSviewer 1.6.19 were used to analyze the literature related to airway remodeling. After time slicing and thresholding, modeling, pruning, merging and other steps, information such as country, institution, journal, author, author unit, and keywords were extracted for analysis [11]. The results are presented graphically or in tabular form, where nodes represent different elements and node size reflects the number or frequency of different elements. Links between nodes represent relationships, including collaboration, co-occurrence, or coreference. The colours of nodes and connections represent different clusters or years. The centrality index was used to evaluate the importance of each node. In a network graph, A node with high centrality indicates that it is a connecting hub of two node sets or highly connected to other nodes. The purple outer ring reflects nodes with centrality greater than 0.1, and the red point represents the citation/frequency burst. Microsoft Excel 365 was also used for data analysis.

3. Results

3.1. General data

From January 1, 2004 to June 3, 2023, 4077 articles were published. The authors came from 76 countries. Airway remodeling, as a classic research field of the respiratory system, has shown a steady increase in the annual number of documents issued in the past 20 years, with an average number of 179.7 documents issued from 2004 to 2022, of which the year with the most published literature is 2021 (Fig. 1).

3.2. Categorization of published articles based on country, region, and institution

The national cooperative network was plotted according to the parameters in Fig. 2 (N = 76, E = 88, Density = 0.0309). In further analysis, we extracted the top 20 countries, including 12 from Europe, 5 from Asia, 2 from North America, 1 from South America, 1

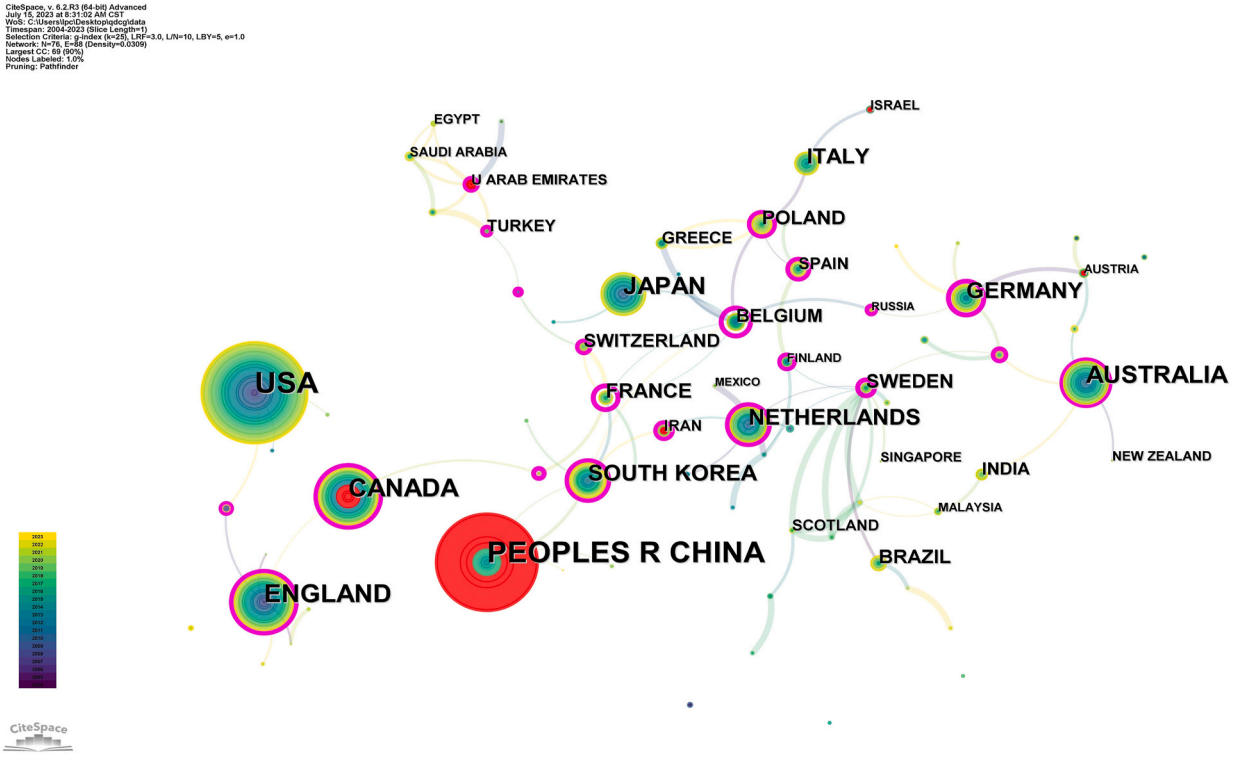

Fig. 2. Co-operation among countries that published airway remodeling-related studies.

from Oceania, 1 from Africa, the United States (n = 951, centrality index = 0.10) and China (n = 913, centrality index = 0.10) with the highest proportion of documents issued. Judging from the annual issuance volume, among the top 20 countries in the publication volume, the United States ranks first, and China is the country with the fastest increase in the publication volume, with the strongest citation bursts. However, the centrality index is low, indicating that its academic influence in airway remodeling needs to be improved. In contrast, European countries represented by Germany, Italy, France, Poland, Spain, Greece, etc., have a more significant academic influence in airway remodeling and have formed a stable national cooperative group. Furthermore, we have independently graphed the yearly circulation figures of the foremost six nations. (Figs. 2 and 3).

Institutional cooperative network maps were generated using Citespace (n = 473, E = 720, Density = 0.0064) (Fig. 4). Among the top 20 sites for publication, 8 were from Europe, 7 from America, 3 from Oceania, and 2 from Asia, of which 3 institutions, RLUK-Research Libraries UK (England), Imperial College London (England), and the University of California System (USA), contributed the highest number of publication volume (Fig. 5A). In addition, the top 25 institutions with the strongest citation bursts were generated according to the preset parameters (Fig. 5B), of which 13 were located in Asia, 4 in North America, 2 in Europe, and 1 in Oceania, and so far, 10 institutions are still in a state of burst growth in the number of publication volume, which shows that airway remodeling as a classic topic of the respiratory system still has great exploration value in recent years. In addition, it is particularly explained that 12 institutions come from China. However, few high-quality research papers are published by these institutions, which shows that Chinese scholars have a weak research foundation in this area and still need in-depth study and co-operation and sharing.

3.3. Distribution of fields of study

Pie chart of study area distribution based on analytical data (Fig. 6). RESPIRATORY SYSTEM (n = 1069), IMMUNOLOGY (n = 875),

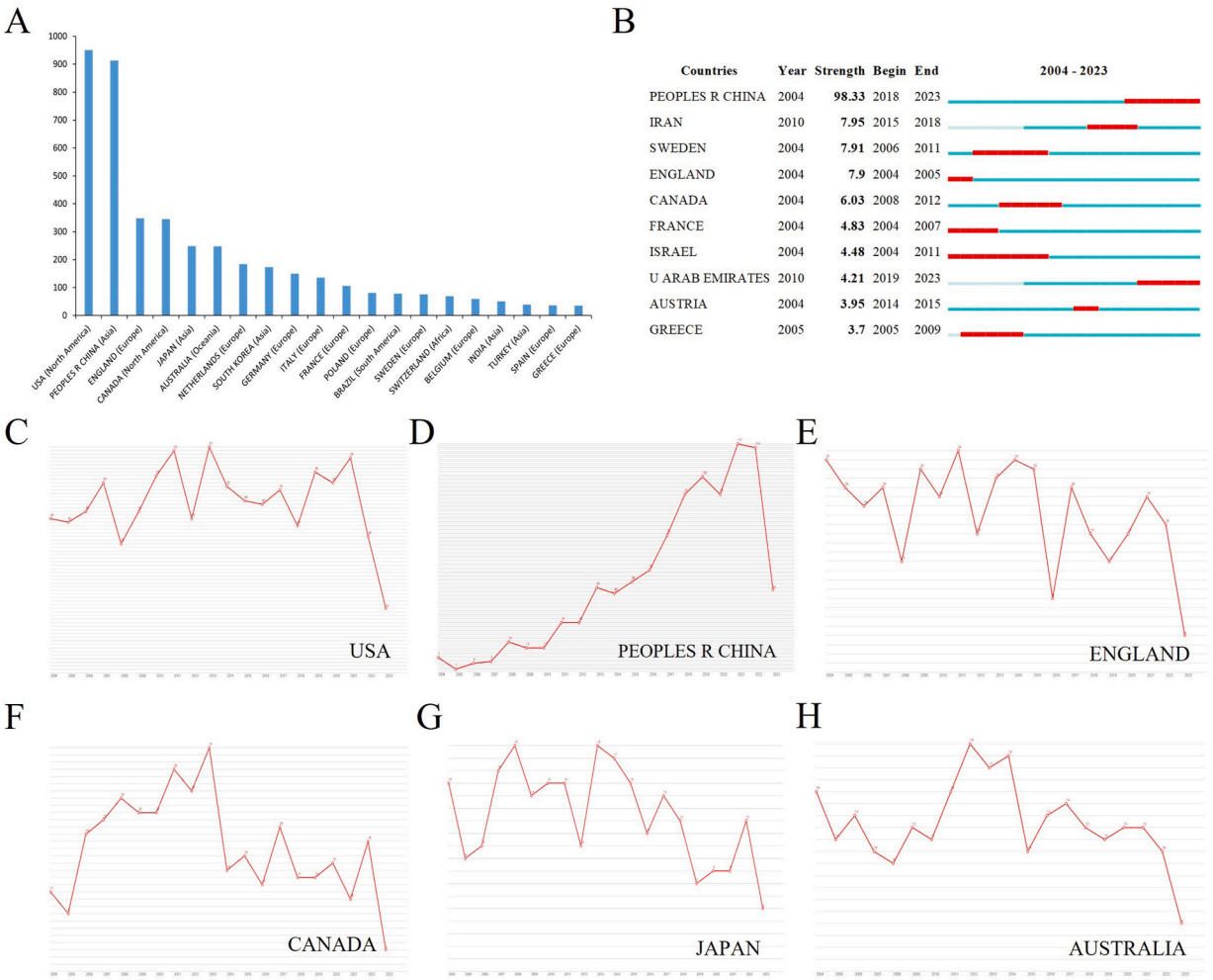

Fig. 3. Co-operation among countries that published airway remodeling articles-related studies. A: Top 20 countries that published airway remodeling articles-related studies; B: top 10 countries with the strongest citation bursts; C–H: Annual number of airway remodeling-related studies in each country. The red colour shown on the right side of Fig. 3B indicates that references were highly cited in a short period.

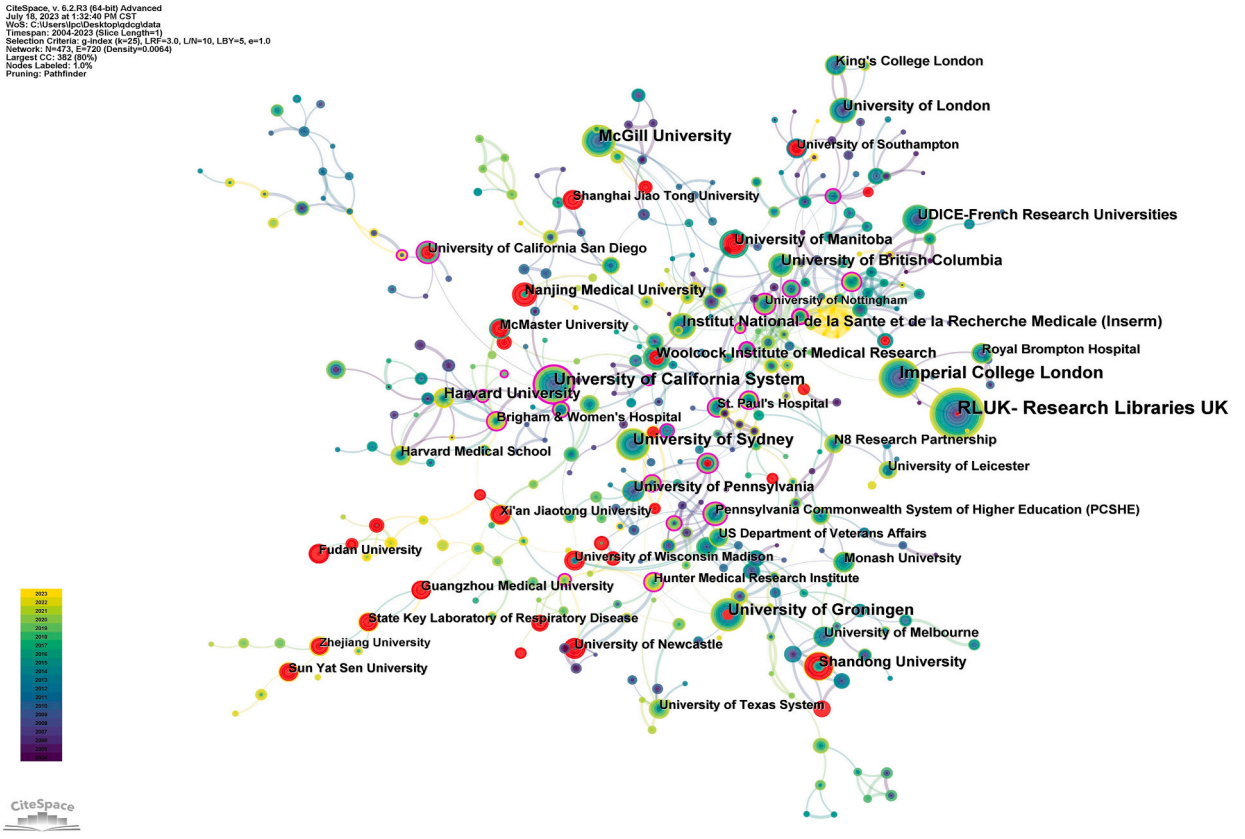

Fig. 4. Co-operation among institutions that published airway remodeling-related studies.

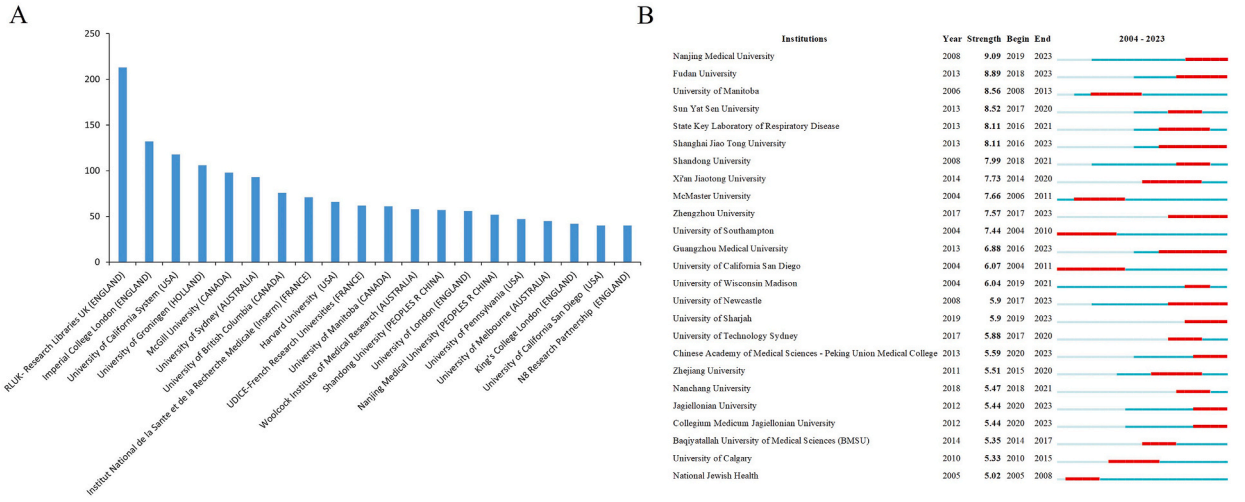

Fig. 5. Top institutions that published airway remodeling-related studies. A: Top 20 institutions publishing in airway remodeling-related studies; B: Top 25 institutions with the strongest citation bursts that published airway remodeling-related studies. The red colour shown on the right side of Fig. 5B indicates that references were highly cited in a short period.

and ALLERGY (n = 566) together accounted for 42.39 % of the study area. Disciplines such as Cell Biology, Biochemistry & Molecular Biology, Physiology, Critical Care Medicine, Oncology, Pathology, Cardiac& Cardiovascular Systems, Radiology, Nuclear Medicine& Medical Imaging, Endocrinology& Metabolism were also included. The subject coverage is broad, and the side shows that the mechanism involved in airway remodeling is complex and requires further future research.

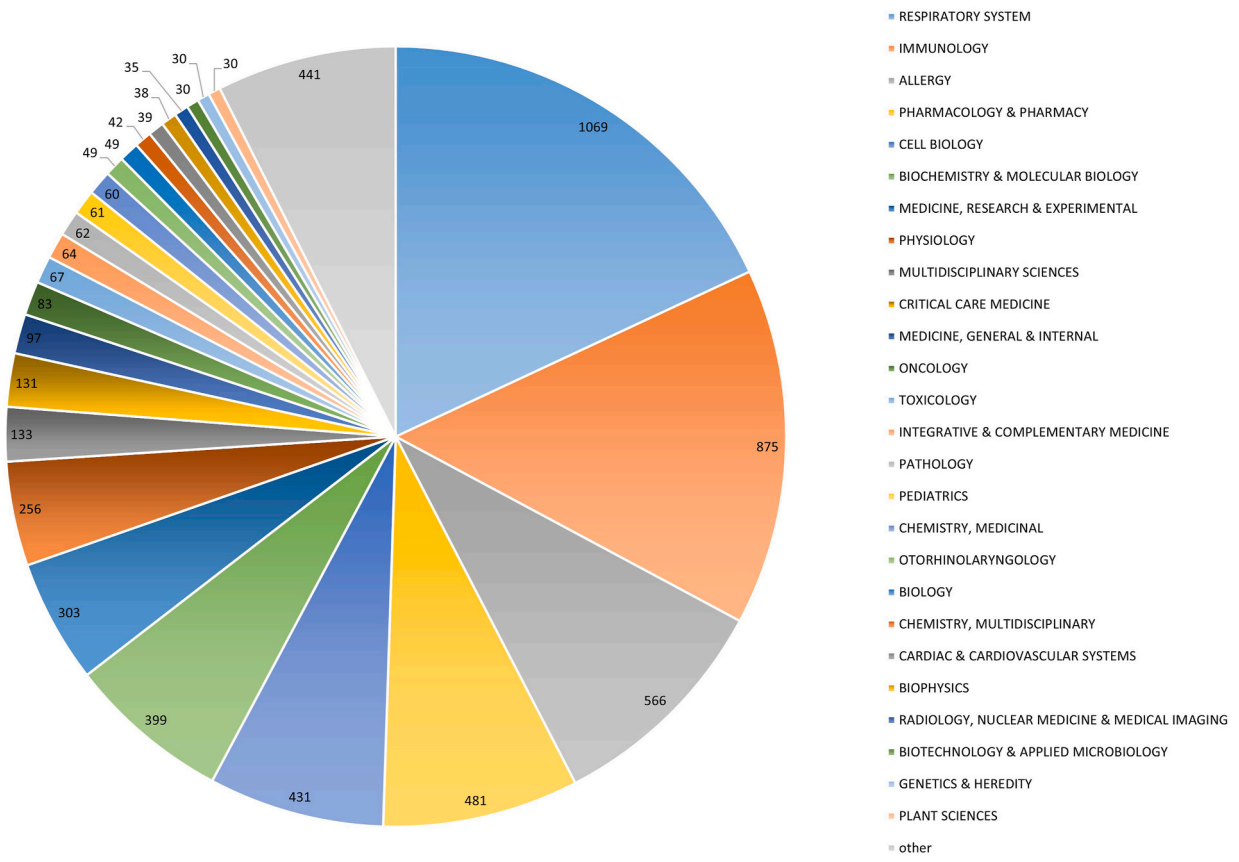

Fig. 6. Research areas of airway remodeling-related studies.

3.4. Authors' collaborations

As shown in Fig. 7, Each point represents an author and has a colour that indicates the density of items at that point. The larger the number of items in the neighborhood of a point the closer the colour of the point is to yellow. We found that most of the authors with high yields of papers had stable collaborators and created a fixed research team. Halayko Andrew J, Hamid Qutayba, and Gosens Reinoud's team had the most significant number of publications and academic influence in this field. Among them, the main direction of Halayko Andrew J's team is the Role of Th17 cytokines in airway remodeling, and non-canonical WNT-5A signalling regulates airway smooth muscle cell proliferation [12,13].

3.5. Citations

3.5.1. Author Co-citation analysis

Among the top 10 cited authors in frequency (Table 1), Holgate ST was highly involved in airway epithelial cells and airway remodeling in asthma. The main mechanisms involve EMT induced by transforming growth factor-beta1 [14], IL-33 [15] and $CD4^+$ lymphocytes [16], and are committed to clinical studies of related therapeutic targets. Barnes PJ focused on studies of Th2-type asthma and found that Th17 cell infiltration in the airways of asthmatic patients was associated with T cell activity and neutrophil inflammation and may lead to airway remodeling [17,18]. Among the top 10 cited authors in the centrality index (Table 1), those cited more frequently than 100 included Haldar P, Castro M, and Busse WW. Busse WW has high participation in COPD and asthma and found that the IL-33-amphiregulin-osteopontin axis is a potential target for treating fibrosis induced by chronic allergic diseases [19]. In summary, we found that many influential authors have participated in the study of the relationship between Th2 cells and obstructive pulmonary disease to varying degrees, suggesting the important value of Th2 cells in pulmonary diseases [20,21]. In addition, we listed the top 20 influential authors by Burst detection (Fig. 8).

3.5.2. Journal and journal Co-citation analysis

The top five cited journals were AM J RESP CRIT CARE (IF = 24.7), J ALLERGY CLIN IMMUN (IF = 14.2), AM J RESP CELL MOL (IF = 6.4), EUR RESPIR J (IF = 24.3), and J IMMUNOL (IF = 4.4), and the top 5 journals accounted for 12.98 % of the total number of journals related to airway remodeling. Journals cited more than 100 in the top 10 centrality index included TOXICOL APPL PHARM

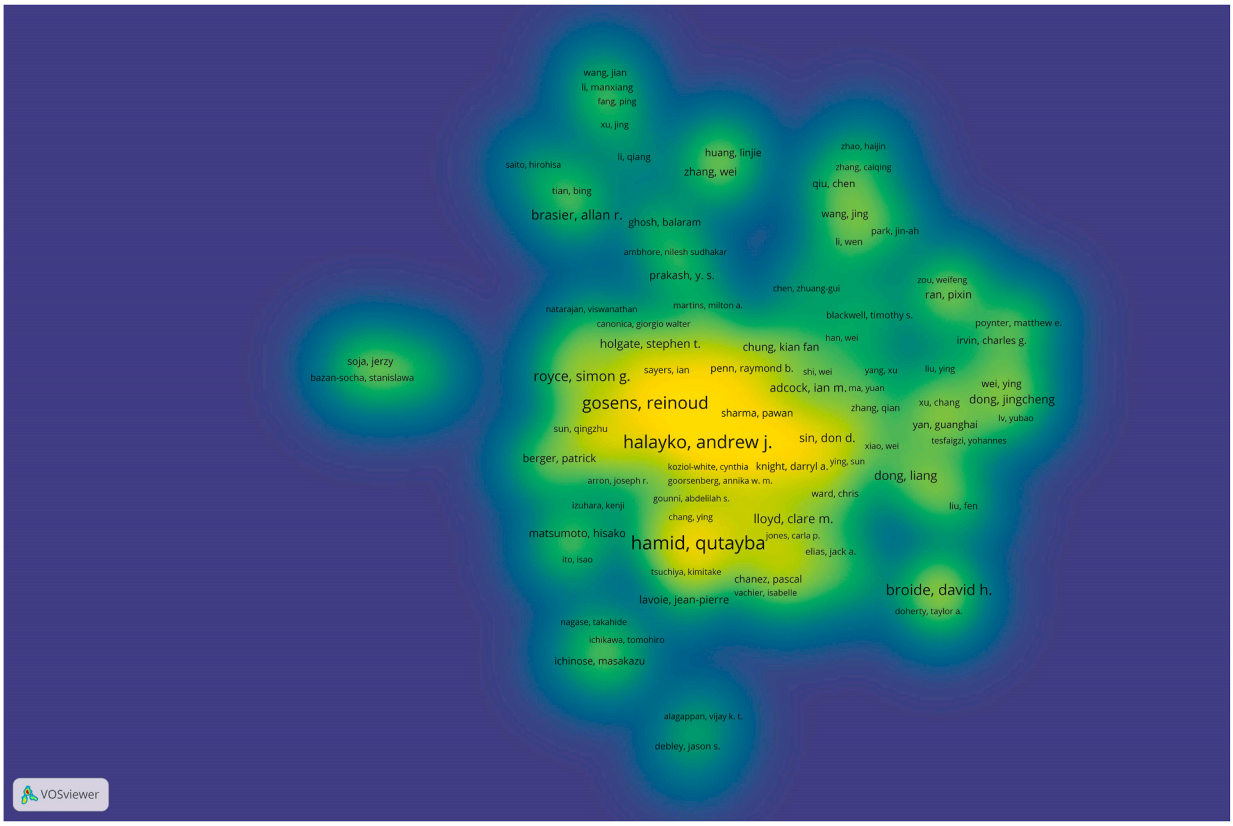

Fig. 7. Co-operation among authors that published airway remodeling-related studies.

Table 1
The top 10 Cited authors of airway remodeling-related studies by frequency and centrality.

No	Cited author	Frequency	Cited author	Centrality
1	HOLGATE ST	549	HOGAN SP	1.11
2	BARNES PJ	541	BLEECKER ER	0.99
3	BOUSQUET J	451	HALDAR P	0.97
4	VIGNOLA AM	386	MATTOS W	0.96
5	JEFFERY PK	373	CASTRO M	0.93
6	HOSHINO M	367	BUSSE WW	0.92
7	JAMES AL	334	BRUSSELLE GG	0.91
8	ANONYMOUS	330	NAIR P	0.9
9	BOULET LP	308	CORRY DB	0.9
10	WENZEL SE	308	GUPTA S	0.89

(IF = 3.8) and MEDIAT INFLAMM (IF = 4.6). The above journals basically cover the leading journals of the respiratory system, indicating that the field of airway remodeling has an unshakable position in the primary and clinical research of the respiratory system (Table 2).

Furthermore, a dual-map overlay of journals was constructed to display the citation relationship of journals. Where the citing journals are shown on the left, while the cited journals are shown on the right. The results showed that the journals publishing airway remodeling-related literature mainly focused on Molecular, Biology, Immunology and Medicine, Medical, Clinical, while the journals that had an impact on their development mainly distributed in Molecular, Biology, Genetics and Health, Nursing, Medicine. Four primary citation relationships were formed, Molecular, Biology, Immlogy - Molecular, Biology, Genetics (z-score = 8.66), Medicine, Medical, Clinical - Molecular, Biology, Genetics (z-score = 4.27), Molecular, Biology, Immunology - Health, Nursing, Medicine (z-score = 2.47) and Medicine, Medical, Clinical - Health, Nursing, Medicine (z-score = 1.92) (Fig. 9).

3.5.3. Reference Co-citation analysis

The timeline of the cluster network of reference was plotted according to the parameters in Fig. 10 (Q = 0.8414; S = 0.9385). Among 3594 articles, 98,313 citations were recorded, achieving 25 clusters for the overall data. The details of clustering are shown in

Cited Authors	Year	Strength	Begin	End	2004 - 2023
FEHRENBACH H	2018	42.42	2019	2023	
LAMBRECHT BN	2004	38.42	2014	2023	
PRAKASH YS	2014	38.09	2017	2023	
PAPI A	2011	32.8	2018	2023	
HIROTA N	2016	32.12	2016	2023	
HOUGH KP	2021	28.68	2021	2023	
LIU Y	2016	28.21	2016	2023	
HALWANI R	2011	24.54	2013	2021	
AL-MUHSEN S	2013	23.25	2013	2023	
WANG J	2018	23.06	2018	2023	
ROYCE SG	2012	22.88	2014	2019	
GLOBAL INITIATIVEFORASTHMA	2015	21.85	2017	2023	
GRAINGE CL	2012	21.8	2012	2021	
ZHANG Y	2018	21.4	2020	2023	
HANANIA NA	2017	21.27	2017	2023	
SOHAL SS	2016	19.62	2016	2023	
CORREN J	2012	19.3	2013	2023	
GIRODET PO	2013	19.03	2015	2020	
LIU L	2019	18.83	2019	2023	
GREGORY LG	2013	18.66	2013	2019	
MCMILLAN SJ	2005	18.58	2007	2011	
WANG Y	2014	18.5	2019	2023	
THOMSON NC	2018	18.24	2018	2023	
LI Y	2017	18.17	2017	2023	
CASTRO M	2012	18.11	2016	2023	

Fig. 8. Top 25 Cited Authors with the Strongest Citation Bursts. The red colour shown on the right side of the figure indicates that references were highly cited in a short period.

Table 3, mainly including obstructive airway diseases, bb-treated airway diseases (PDGF-BB-treated airway smooth muscle), allergen-induced airway remodeling, extracellular matrix, non-coding RNA, lung diseases, computed tomography, treating severe asthma, clinical pathogenesis and epithelial-to-mesenchymal transition (epithelial-to-mesenchymal transition). Clustering #0 (obstructive airway diseases) is the most significant and emerging cluster that deserves our particular attention. We conducted an in-depth analysis of the representative literature in cluster#0. Seventeen papers in this cluster were cited in articles published in 2022 by Gilda Varricchi et al. [22]. The authors concluded that introducing biologics in severe asthma completely normalised previously thought irreversible airflow obstruction in some patients. Therefore, it is of great clinical importance to distinguish 'fixed' airflow obstruction due to structural changes unresponsive to current therapies from a "reversible" one. The Aileen team came up with their views on assessing airway remodeling, and the authors highlight the potential of computed tomography and magnetic resonance imaging and propose the possibility of utilizing volumetric imaging tools to assess the heterogeneity of airway remodeling throughout the lung [23]. In addition, Andrea et al. investigated the potential of KL-6 as a potential serum biomarker in severe asthma with fixed airway obstruction [24].

Table 2
The top 10 cited journals of airway remodeling-related studies by frequency and centrality.

No	Cited journals	Frequency	Cited journals	Centrality
1	AM J RESP CRIT CARE	3020	TOXICOLOGY	1.16
2	J ALLERGY CLIN IMMUN	2707	TOXICOL APPL PHARM	1.04
3	AM J RESP CELL MOL	2383	GENOME BIOL	0.93
4	EUR RESPIR J	2259	GENOME RES	0.89
5	J IMMUNOL	1890	ANNU REV PHARMACOL	0.88
6	AM J PHYSIOL-LUNG C	1879	MEDIAT INFLAMM	0.86
7	THORAX	1852	FRONT BIOSCI-LANDMRK	0.86
8	CHEST	1744	ASTHMA	0.86
9	CLIN EXP ALLERGY	1708	CANCER METAST REV	0.84
10	J CLIN INVEST	1611	CURR OPIN STRUC BIOL	0.84

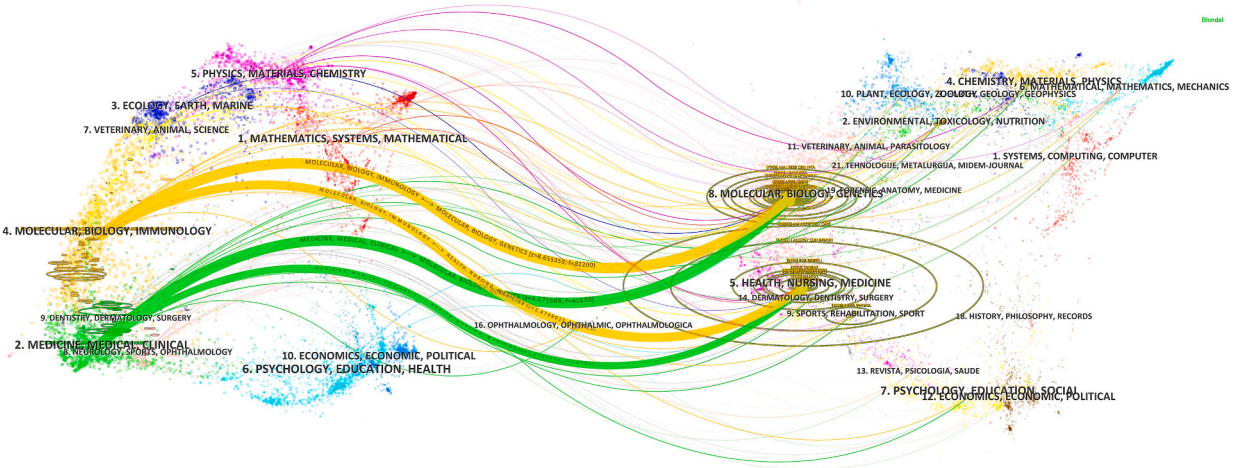

Fig. 9. The dual-map overlay of journals on airway remodeling-related studies.

PDGF-BB, which is mentioned in cluster #1 (PDGF-BB-treated airway smooth muscle), has emerged as a pivotal factor in the realm of airway remodeling, particularly in the context of asthma pathogenesis. Several recent studies underscore the multifaceted influence of PDGF-BB on airway smooth muscle cells (ASMCs), inflammation, and cellular mechanisms associated with asthma. Quan et al. provided substantive insights into the stimulatory effects of PDGF-BB on the proliferation and migration dynamics of human ASMCs, accentuating the potential roles of circ_0002594 and TRIM8 in the progression of asthma, thereby adding layers of complexity to our understanding of PDGF-BB's influence [25]. In a complementary vein, Feng et al. shed light on the therapeutic implications by identifying exosomal miR-301a-3p from ADSCs as a modulator capable of suppressing PDGF-BB-induced proliferation and migratory tendencies in ASMCs [26]. Turning attention to the role of estrogen receptors (ERs), Bhalamudi et al. elucidated the differential impacts of ER subtypes, with particular emphasis on ERβ, in orchestrating airway remodeling processes. Their investigations revealed that the activation of ERβ can modulate calcium responses within inflamed ASM cells, thus substantiating its potential contribution to airway relaxation mechanisms [27]. In a related scholarly endeavor, Ambhore et al. expanded upon these findings by demonstrating that ER-β activation might attenuate extracellular matrix (ECM) deposition, invoking the NF-κB pathway as a potential mechanistic underpinning [28]. Furthermore, the investigative work by Liu et al. delved into the implications of 17β-Estradiol (E2) in orchestrating apoptosis within ASMCs. Their findings offer nuanced perspectives on potential intersections between E2-mediated signalling cascades and those activated or modulated by PDGF-BB, thereby enriching our comprehensive understanding of these complex biological pathways [29]. In summary, the multifaceted roles attributed to PDGF-BB furnish pivotal insights into the intricacies of airway remodeling in asthma, setting a robust foundation for pioneering therapeutic interventions that target these intricate pathways.

In addition, allergen-induced airway remodeling (Cluster#2) is widely used as a classical animal model of airway remodeling, and the earliest documented literature dates back to 1985. Cluster#4 also deserves our attention. With the development of second-generation sequencing technology, non-coding RNA has shown a rapid growth trend in the field of airway remodeling, and is expected to become a new serum biomarker [30–32]. Alternatively, burst detection and top co-citation articles may also have a suggestive role for future development trends (Fig. 11, Table 4).

3.6. Analysis of keywords

The Co-occurrence network was mapped when combining keywords with the same meaning (N = 661, E = 950, Density = 0.0044)

Fig. 10. Co-citation analysis of airway remodeling-related studies. The results of clusters are shown on the right side. The colour represents when the cluster appears. The red point represents the citation/frequency burst.

Table 3
Co-citation clustering of airway remodeling-related studies.

Cluster	Size	Silhouette	Mean (Year)	Label (LLR)
0	58	0.869	2019	obstructive airway diseases
1	57	0.855	2019	bb-treated airway
2	56	0.976	2003	allergen-induced airway remodeling
3	49	0.974	2003	extracellular matrix
4	43	0.821	2018	non-coding rna
5	41	0.869	2012	lung diseases
6	41	1	2001	computed tomography
7	40	0.921	2012	treating severe asthma
8	40	0.924	2014	pathogenesis clinical feature
9	40	0.986	2011	smooth muscle
10	38	0.981	2008	akt pathway
11	34	0.961	2017	severe asthma
12	33	0.955	2008	mucosal bromodomain-containing protein
13	30	0.995	2016	mesenchymal stem cell
14	29	0.954	2010	traditional Chinese medicine
15	28	0.962	2019	mast cell
16	28	0.939	2005	human fetal airway
17	27	0.916	2016	therapeutic target
18	27	0.947	2011	vascular endothelial growth factor
19	25	1	2003	muscarinic receptor
20	25	0.968	2007	bronchial thermoplasty
21	22	0.968	2015	rhinovirus infection
22	21	0.953	2006	glucagon-like peptide-1 receptor agonist
23	19	0.939	2020	rat airway
24	10	1	2013	smooth muscle
25	8	0.996	2011	akt pathway

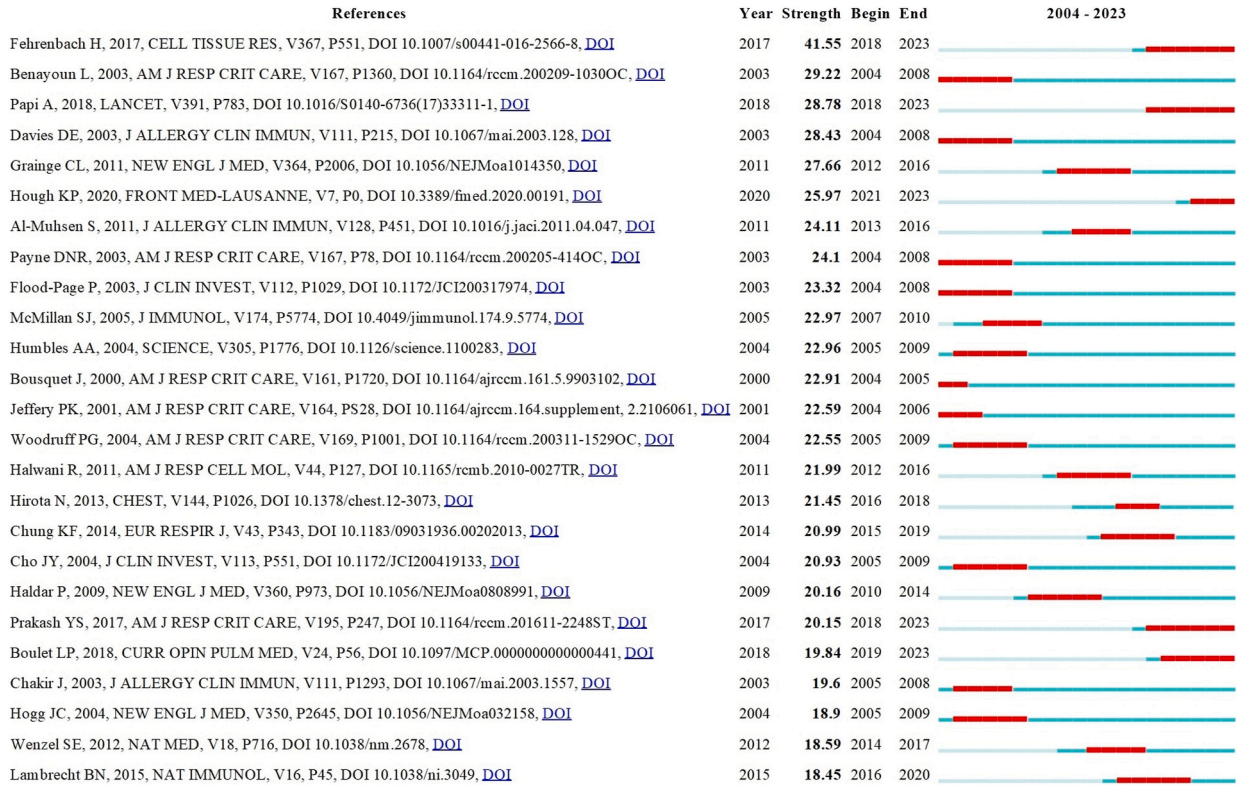

Fig. 11. Top 25 References with the Strongest Citation Bursts. The red colour shown on the right side of the figure indicates that references were highly cited in a short period.

Table 4
The top 5 co-citation airway remodeling-related studies.

No	Author	frequency	Summary
1	Fehrenbach H [45]	88	the phenotype/endotype concept of asthma; Quantitative approaches to assess airway remodeling; airway remodeling may alternatively evolve as a primary event initiated very early in life in the absence of any symptoms or of any detectable inflammation.
2	Benayoun L [75]	75	fibroblast accumulation and ASM hypertrophy in proximal airways are selective determinants of severe persistent asthma.
3	Davies DE [76]	73	ADAM33 is an asthma susceptibility gene, the expression of which is abundant in airway fibroblasts and smooth muscle but absent from T lymphocytes or inflammatory cells that infiltrate the airway wall in patients with asthma
4	Papi A [77]	69	The author provides a clinically focused overview of asthma, including epidemiology, pathophysiology, clinical diagnosis, asthma phenotypes, severe asthma, acute exacerbations, and clinical disease management in adults and children older than 5 years. Emerging therapies, controversies, and uncertainties in asthma management are also discussed.
5	Payne DNR [78]	62	RBM thickening is already present in children with difficult asthma and to a similar extent to that seen in adults with asthma. In addition, we find no association with age, symptom duration, lung function, or concurrent eosinophilic airway inflammation.

(Fig. 12). We found that the most frequently cited keywords included airway remodeling, expression, inflammation, asthma, airway inflammation, cells, activation, obstructive pulmonary disease, murine model, and airway smooth muscle, reflecting the importance of airway remodeling in airway chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease (Table 5). A total of 21 items were obtained by cluster analysis (Fig. 13, Table 6), including t cells, inhaled corticosteroids, airway smooth muscle, barrier function, mesenchymal stem cells, and computed tomography. After further classification of the clustering information, it was found that the central effector cells associated with airway remodeling included t cells, airway smooth muscle (cells), mesenchymal stem cells, and mast cells, and the molecular mechanisms associated with airway remodeling included epithelial-mesenchymal transition, matrix metalloproteinases, allergic airway inflammation, and (tumour) necrosis factor-alpha, Cluster#5 computed tomography suggests that imaging remains the primary modality in the assessment of airway remodeling.

"Burst items" represents words that have been frequently cited for a period of time, and burst keywords show cutting-edge themes and critical areas of research. The table lists the first 30 burst keywords (Fig. 14). Combined with the co-occurrence analysis of

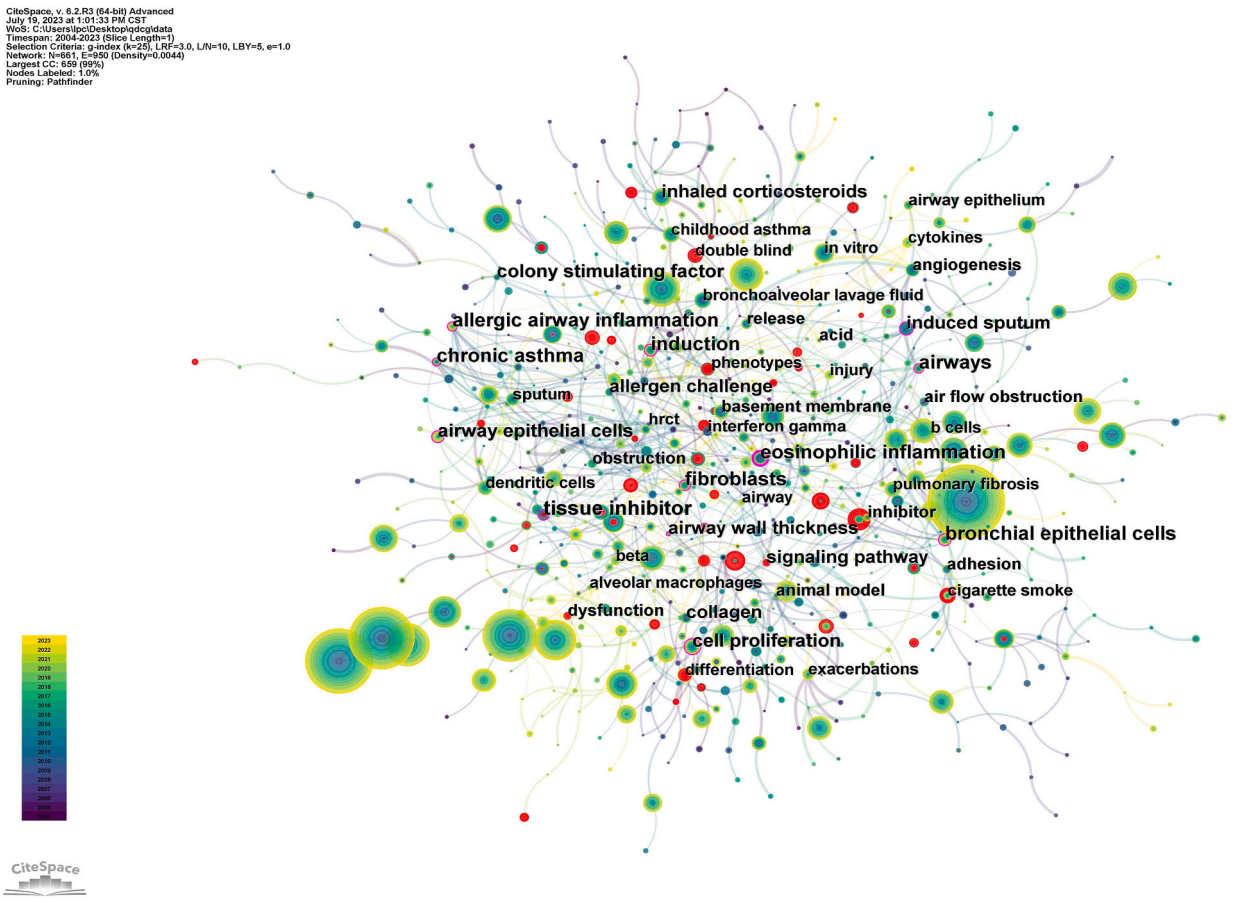

Fig. 12. Co-occurrence network of airway remodeling keywords.

Table 5
The top 20 keywords of airway remodeling-related studies.

Rank	Frequency	Centrality	Keywords
1	1176	0	airway remodeling
2	919	0	expression
3	834	0.01	inflammation
4	660	0	asthma
5	439	0	airway inflammation
6	403	0	cells
7	325	0.01	activation
8	322	0.01	obstructive pulmonary disease
9	283	0.03	murine model
10	272	0.02	airway smooth muscle
11	271	0.02	disease
12	259	0.01	smooth muscle
13	233	0.01	lung
14	231	0.02	hyperresponsiveness
15	230	0.01	proliferation
16	228	0.01	growth factor beta
17	222	0.02	lung function
18	221	0	gene expression
19	210	0.01	mice
20	210	0	tgf beta

keywords in the previous text, we found that the early research on airway remodeling mainly focused on asthma, and the research direction was predominantly clinical and pathological phenomena, mainly including subepithelial fibrosis, bronchial hyperresponsiveness, and basement membrane. There were few and no in-depth studies on the specific molecular mechanism. In recent

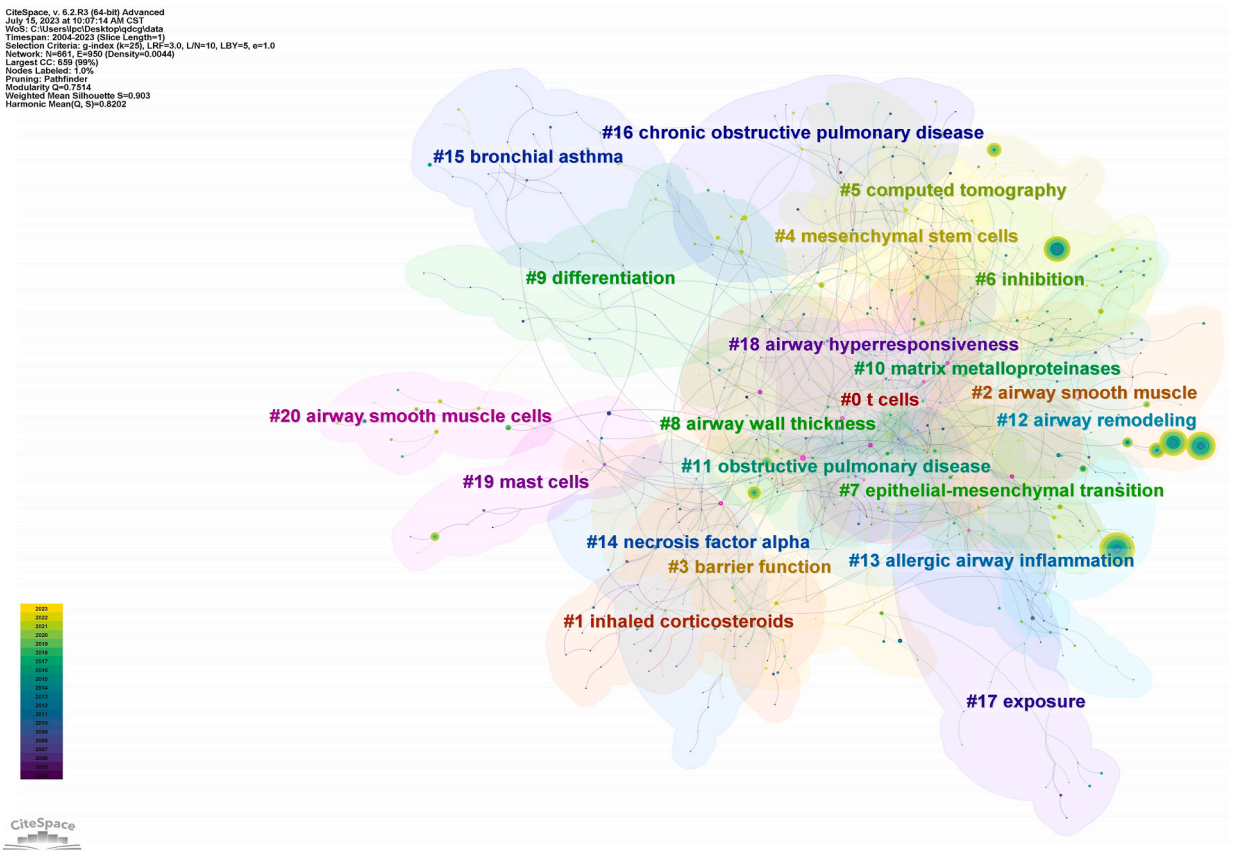

Fig. 13. Clustering network of airway remodeling keywords.

Table 6
Clustering of keywords in airway remodeling-related studies.

Cluster	Size	Silhouette	Mean (Year)	Label (LLR)
0	50	0.88	2010	t cells
1	45	0.941	2009	inhaled corticosteroids
2	43	0.912	2009	airway smooth muscle
3	41	0.874	2012	barrier function
4	41	0.84	2011	mesenchymal stem cells
5	40	0.909	2011	computed tomography
6	37	0.864	2012	inhibition
7	34	0.886	2011	epithelial-mesenchymal transition
8	34	0.938	2010	airway wall thickness
9	33	0.832	2011	differentiation
10	31	0.928	2009	matrix metalloproteinases
11	29	0.896	2008	obstructive pulmonary disease
12	28	0.978	2012	airway remodeling
13	28	0.881	2010	allergic airway inflammation
14	27	0.899	2009	necrosis factor alpha
15	25	0.956	2010	bronchial asthma
16	24	0.927	2011	chronic obstructive pulmonary disease
17	23	0.936	2012	exposure
18	19	0.922	2008	airway hyperresponsiveness
19	15	0.885	2008	mast cells
20	12	1	2009	airway smooth muscle cells

years, the study of airway remodeling has gradually expanded from asthma to COPD and cancer, and the research on pathogenesis has also increased significantly, mainly involving epithelial-mesenchymal transition, autophagy, oxidative stress and so on. Double blind (trial) cited rapidly increased from 2017 to 2023, indicating that the study on airway remodeling has developed from simple basic research to the stage of clinical trials, suggesting that we will have more treatment strategies for airway remodeling to benefit patients

Keywords	Year	Strength	Begin	End	2004 - 2023
oxidative stress	2008	**18.73**	2020	2023	
epithelial-mesenchymal transition	2012	**15.68**	2017	2023	
endothelial growth factor	2005	**14.48**	2005	2010	
subepithelial fibrosis	2004	**13.29**	2004	2008	
bronchial hyperresponsiveness	2004	**12.99**	2004	2010	
basement membrane	2004	**12.83**	2004	2007	
copd	2006	**11.29**	2018	2023	
up regulation	2005	**10.94**	2005	2010	
bronchoalveolar lavage	2004	**10.9**	2004	2010	
mild asthma	2004	**10.7**	2004	2010	
necrosis factor alpha	2005	**10.7**	2005	2009	
risk	2016	**10.37**	2016	2023	
signal transduction	2004	**10.27**	2004	2009	
human lung fibroblasts	2005	**9.98**	2005	2008	
extracellular matrix proteins	2005	**9.94**	2005	2013	
fluticasone propionate	2004	**9.93**	2004	2012	
cancer	2011	**9.57**	2016	2023	
messenger rna expression	2005	**9.53**	2005	2009	
vascular endothelial growth factor	2005	**9.25**	2005	2008	
double blind	2005	**9.06**	2017	2023	
messenger rna	2004	**8.72**	2004	2010	
promotes	2018	**8.61**	2018	2021	
mesenchymal transition	2015	**8.59**	2018	2023	
epithelial mesenchymal transition	2011	**8.54**	2017	2023	
tissue inhibitor	2004	**8.42**	2004	2010	
differentiation	2006	**8.37**	2017	2021	
safety	2017	**8.23**	2017	2020	
transforming growth factor beta 1	2004	**7.98**	2004	2007	
bronchial thermoplasty	2009	**7.82**	2017	2023	
autophagy	2019	**7.81**	2019	2023	

Fig. 14. Top 30 Keywords with the Strongest Citation Bursts. The red colour shown on the right side of the figure indicates that references were highly cited in a short period.

in the future, The cited volume of bronchial thermoplasty also increased synchronously in 2017–2023, confirming this view. The above information suggests the development direction of the field of airway remodeling in the future.

4. Discussion

Airway remodeling refers to the structural and functional changes of airway tissue caused by repeated chronic inflammatory stimulation injury and an incomplete repair, which is more common in chronic airway inflammatory diseases such as asthma and COPD [33]. It is a significant cause of irreversible airway stenosis and airflow limitation. In recent years, molecular mechanisms and clinical research on airway remodeling have developed rapidly, but the prevalence, disability rate and mortality of diseases with airway remodeling as the primary manifestation, such as asthma and chronic obstructive pulmonary disease, remain high [34,35]. Through bibliometric analysis by CiteSpace and Vosviewer, the research progress of airway remodeling can be understood to more accurately predict the future research direction [36].

The number of publications can reflect the overall development trend in this field. From 2004 to 2023, the number of publications related to airway remodeling has been increasing, which indicates that the area of airway remodeling has been continuously concerned by clinicians and relevant researchers for nearly two decades (Fig. 1). Judging from the number of national research articles, the United States has the largest number of research articles, highlighting the country's attention to the field of airway remodeling (Fig. 3A). In addition, airway remodeling has experienced an explosive increase in the number of research articles in China, Canada, the United Arab Emirates and Iran, suggesting that airway remodeling has made breakthroughs in these countries (Fig. 3B). Among them, China has been the fastest-growing country in literature publication in recent years and will still present a rapid progress trend in the next few years, suggesting that China will play a more critical role in the field of airway remodeling in the future (Fig. 3D). In the past two decades, the majority of the top 20 institutions in terms of the number of research articles came from Europe (n = 8) and North America (n = 7), but the majority of the countries with the fastest growth rate in the number of literature publications were distributed in Asia, indicating that Asia is quickly catching up with Europe and North America in this field, but its disciplinary influence is generally small and it still takes a long time to develop. Although the United States and China have produced the most significant number of articles, their co-operation is not close, and enhancing co-operation in this area could contribute to groundbreaking results (Fig. 2).

In the analysis of co-citation authors in airway remodeling, Holgate ST, Barnes PJ, Bousquet J, Haldar P, Castro M and Busse WW contributed the most. Burst detection demonstrates that Fehrenbach H, Lambrecht BN, Prakash YS, Papi A and Hirota N are star authors in the field of airway remodeling in recent years and have a leading position in the research direction in the future (Fig. 8). In recent years, the Fehrenbach H team has concluded that targeting JNK and FoxO signalling in the airways could efficiently interfere with disease-associated airway remodeling processes through a matching drosophila model [37]. While Lambrecht et al. worked on allergic airway inflammation all year round [38,39].

Journals with a high volume of publications and high co-citation provide the necessary information for authors to select high-quality journals [40]. Studies have shown that various journals have published articles related to airway remodeling, of which highly cited journals are relatively concentrated (Fig. 9). most of the top 10 journals came from JCR Q1 or Q2, and most of them are top journals in respiratory-related fields (Table 2), such as AM JRESP CRIT CARE, J ALLERGY CLIN IMMUN, AM J RESP CELL MOL, EUR RESPIR J and J IMMUNOL, indicating that airway remodeling is an important pathological process in respiratory diseases and top scholars have shown a strong interest in this topic. Therefore, paying more attention to these journals is essential to obtain new research advancements or discoveries.

The analysis of references has revealed significant advancements in the understanding of airway remodeling over the past 20 years. The timeline of the cluster network of reference suggests that non-coding RNA (ncRNAs), the PI3K-AKT pathway, and glucagon-like peptide-1 receptor agonists have garnered significant attention in recent years (Fig. 10). ncRNAs, known to regulate gene expression and play a crucial role in cell differentiation, proliferation, and apoptosis, have been linked to various diseases. Specifically, the lncRNA-miRNA-mRNA axis has been validated in chronic inflammation and airway remodeling of asthma [41]. Intervention in the expression of non-coding RNAs has yielded promising results in influencing airway remodeling [42,43], providing new directions for improvement or reversal of airway remodeling. In addition to these findings, recent studies have highlighted the pivotal role of sex steroids, particularly estrogen and its receptors, in regulating the inflammatory environment and airway remodeling. Liu et al. demonstrated the dual effects of 17β-Estradiol (E2) on cell apoptosis under pathological conditions, mediated by the CD38/SIRT1/p53 signalling pathway [29]. Bhallamudi et al. found that specific ERβ activation reduces intracellular calcium in inflamed ASM cells, potentially regulating ASM contractility and thereby relaxing airways [27]. Furthermore, Ambhore et al. reported that activation of ER-β diminishes ECM deposition via suppressing the NF-κB pathway activity, suggesting a potential novel target to blunt airway remodeling [28]. These views provide a more comprehensive understanding of airway remodeling. Burst detection indicates that Mesenchymal cells, biomarkers, and noninvasive assessments are emerging research directions in airway remodeling [24,44] (Fig. 11).

Through the analysis of airway remodeling-related literature and keywords, we summarized the following four keywords: (1) Obstructive pulmonary disease: Airway smooth muscle hyperplasia (ASM)/hypertrophy is a marker of airway remodeling and an essential driver of Asthma pathophysiology. Increasing ASM mass leads to bronchial obstruction, decreased lung function, and increased sensitivity to external triggers [22]. ASM mass is estimated to increase 50 %–200 % in patients with non-fatal asthma and 200 %–400 % in patients with fatal asthma [44]. Airway remodeling is present in many obstructive pulmonary diseases, and previous studies suggest that airway remodeling is an event triggered by chronic airway inflammation, but recent studies suggest that airway remodeling may emerge as an initial event, even before triggering any respiratory symptoms and inflammation process [1,45]. Therefore, there are still many mysteries about airway remodeling in obstructive pulmonary disease, and there is currently a lack of effective interventions for airway remodeling in clinical practice, which is one of the most challenging problems in treating respiratory

diseases and is the goal of future treatment [33]. (2) Noninvasively Assessing: Computed tomography (CT) and magnetic resonance imaging (MRI) techniques can accurately assess the three-dimensional lung structure of patients. This noninvasive assessment method bypasses the cumbersome operation and medical ethics of invasive examination. An increasing number of studies have used CT/MRI techniques to qualitatively or quantitatively detect airway remodeling status in patients with asthma or COPD [46]. CT/MRI can also dynamically assess the patient's disease changes and treatment outcomes [47]. It has been shown that MRI using hyperpolarized gases, such as Helium or Xenon, has been used clinically to analyze regional information on the distribution of ventilation in the lungs and has achieved good results [48]. Therefore, non-invasive detection methods represented by CT and MRI have become sharp tools for assessing airway remodeling because of their unique advantages. (3) Inhaled Corticosteroids: Glucocorticoids, the most classical drugs for asthma and COPD, mainly exert strong anti-inflammatory and anti-airway remodeling effects by inhibiting T lymphocytes, neutrophils, macrophages, and eosinophils [49]. The inhaled corticosteroids commonly used in the respiratory system are budesonide and fluticasone [50]. Several studies have shown that glucocorticoids can affect the process of airway remodeling through signalling pathways such as MAPK, EGFR and HIF-1α [51–53]. However, steroid-resistant asthma is also common in clinical practice, suggesting the existence of intrinsic mechanisms that do not rely on inflammation and directly induce airway remodeling [54]. Therefore, analyzing the mechanism of airway remodeling and its intrinsic relationship with airway inflammation is still an important scientific problem to be solved urgently in the field of respiratory disease research. (4) Clinical Trial: After recent decades of research, scholars have achieved a certain understanding of airway remodeling, and the research theme is also excessive from basic medical research to clinical research, which suggests that we will have more treatment strategies for airway remodeling into clinical practice in the future, and related patients will have more treatment options and better prognosis [55,56].

The analysis of key literature and keywords summarises the following five research hotspots and trends. (1) Risk: Allergens, cigarette smoke, and metal components of the environment are the main risk factors for airway remodeling in patients [57]. However, airway remodeling is characterized by marked genetic heterogeneity and phenotypic complexity, and there remain many unknown risk factors that need to be explored through further large-scale epidemiological assessments [58,59]. (2) Noninvasively Assessing: Traditional histological examination seriously limits the research progress due to complex sampling and medical ethical problems. Therefore, non-invasive detection methods represented by CT and MRI are more readily accepted by patients and have become a sharp tool in airway remodeling [60]. Moreover, with the development of technology, new technologies such as optical coherence tomography and impulse oscillometry have also been gradually applied to the relevant evaluation of airway remodeling, so noninvasively assessing will be a primary focus of future research [61]. (3) Biomarkers: Besides imaging studies, serum biomarkers are essential tests for disease diagnosis and efficacy evaluation [62]. Evidence suggests that galectin-3 is a member of the macrophage scavenger receptor family and maybe a diagnostic and prognostic biomarker in various diseases, and elevated Gal-3 levels have been reported in asthma patients [63]. The chitinase 3-like protein 1 YKL-40 is a secreted glycoprotein typically expressed by macrophages and respiratory epithelial cells [64]. Although the biological role played by YKL-40 in asthma remains unclear, many reports suggest that it is associated with airway remodeling. Kimura et al. assessed the relationship between circulating YKL-40 levels and morphologic changes in the respiratory tract and pulmonary parenchyma and longitudinal progression of airflow limitation in severe asthma patients. They finally found a significant correlation between YKL-40 levels and CT indices of proximal airway remodeling [65]. However, limited by previous detection techniques, the application of airway remodeling biomarkers in airway remodeling has developed late, and mature biomarkers are still lacking in clinical practice. As single-cell transcriptomics develops, it will be crucial to chart possible signalling networks in airway remodeling. These studies' results help generate new reliable diagnostic biomarkers [66]. (4) Epithelial-Mesenchymal Transition: EMT can induce airway epithelial fibrosis and promote smooth muscle hyperplasia and extracellular matrix deposition, destroy the epithelial barrier, and aggravate airway inflammation, which is a crucial step in airway remodeling [67,68]. Azithromycin was found improved airway remodeling by inhibiting the EMT process in OVA-induced asthmatic mice [69]. It involves numerous signalling pathways, including the Dedicator of cytokinesis 2 (DOCK2), EGFR, and PI3K/AKT, and is a hot mechanism in airway remodeling research. (5) Autophagy: Autophagy is the recycling mechanism of all eukaryotic cells and plays a significant role in the physiological activity, metabolism and survival of cells [70,71]. In recent years, much evidence has shown that autophagy is associated with airway remodeling, which reveals the potential of regulating autophagy in treating airway remodeling [72]. As a critical link in mesenchymal to epithelial transition, the connection between autophagy and EMT has been extensively investigated in the field of cancer and has also gained attention in airway remodeling [73]. Studies have shown that FSTL1 can promote airway remodeling in asthma by activating autophagy and promoting EMT [74]. In the future, elucidating the mechanism of autophagy activation or inhibition associated with airway remodeling will provide new ideas for diagnosing and treating related respiratory diseases. In addition, for every plus, there is a minus, compared to systemic administration, airway targeting or nanoparticle-based cell targeting approaches will be the direction of future research. It should be pointed out that this study has two significant limitations. First, we only analyzed studies in the WOSCC database. Second, Matthew's effects that could influence the results of bibliometric analysis were not considered.

Our bibliometric analysis has revealed the dynamic and evolving nature of airway remodeling research, with emerging hotspots and trends that hold significant implications for respiratory health. The rapid growth in published literature from China, alongside the United States, highlights the increasing global interest and collaborative efforts in this field. The closer cooperation among European countries suggests potential for more integrated international research efforts, expediting the translation of findings into clinical practice. Our study identified recent research hotspots, such as oxidative stress and epithelial-mesenchymal transition, indicating a shift towards understanding the molecular mechanisms underlying airway remodeling and the development of novel therapeutic strategies. Additionally, the increasing focus on risk factors, noninvasive assessment tools, and biomarkers emphasizes the importance of early detection and prevention in managing respiratory diseases. In summary, our study provides a comprehensive overview of the current status of airway remodeling research between 2004 and 2023, discussing research hotspots and development trends that will

aid scholars and clinicians in understanding the field's development and predicting future research directions.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Pengcheng Liu: Writing – original draft, Visualization, Investigation, Formal analysis. **Yu Wang:** Investigation. **Chen Chen:** Investigation. **Hui Liu:** Investigation. **Jing Ye:** Data curation. **Xiaoming Zhang:** Writing – review & editing. **Changxiu Ma:** Writing – review & editing. **Dahai Zhao:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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