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Research article

Bibliometric analysis of the pirfenidone and nintedanib in interstitial lung diseases

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ABSTRACT

Background: At the beginning of 21st century, reclassification of fibrosing interstitial lung diseases (ILD) scored academic concerning, and then propelled development. Decade before, pifenidone and nintedanib were approved for idiopathic pulmonary fibrosis, but no more drugs are yet available. To evaluate the development traits of pirfenidone and nintedanib in fibrosing ILD, including the influential country, institution, authors, keywords, and the major problems or the priorities of the field emerge and evolve, bibliometric analysis was used to summarize and draw scientific knowledge maps.

Methods: We confined the words to "pirfenidone", "nintedanib", "pulmonary fibrosis", and "lung disease, interstitial". Publications were retrieved from the Web of Science Core Collection on February 24, 2024 with the search strategies. Citespace and VOSviewer were adopted for bibliometric analysis.

Results: For the knowledge map of pirfenidone, a total of 4359 authors from 279 institutions in 58 countries/regions contributed to 538 studies. The United States and Italy are way ahead. Genentech Inc and the University of Turin are the institutions with the strongest influence. AM J RESP CRIT CARE is the maximized influential periodical. Raghu G was the most frequently co-cited scholar. keywords cluster demonstrated that vital capacity, safety, outcome, effectiveness, acute exacerbation, pathway, cell, collagen were the hotspots. The burst timeline of hotspots and references revealed academic transitions of pirfenidone-related studies. About the knowledge map of nintedanib, 3297 authors from 238 institutions in 47 countries/regions published 374 studies. Japan, the United States, and Italy are the most productive countries. Boehringer Ingelheim is the overriding productive institution. New ENGL J MED have important roles in reporting milestones of nintedanib. Richeldi L carried numerous capital publications to support the anti-fibrotic effect of nintedanib. From the network of co-occurrence keywords, idiopathic pulmonary fibrosis, efficacy, and safety were the hotspots. Nintedanib for systemic sclerosis-related ILD and progressive pulmonary fibrosis is the hotspot with sharp evolution recently.

Conclusions: We summarized and showed developmental alterations of pirfenidone and nintedanib in fibrosing ILD through bibliographic index-based analysis. Our findings showed just dozen years sharp development period of pirfenidone and nintedanib in ILD, and identifies potential partners for interested researchers. The burst of hotspots demonstrated the evolvement of research priorities and major problems, and we observed the transition of keywords from

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experimental terms like mouse, bleomycin, cell, pathway, collagen, gene expression, to clinical terms including efficacy, safety, survival, acute exacerbation, and progressive pulmonary fibrosis. In the future, exploration about disparity models of drug administration, differences between early and later initiate anti-fibrotic therapy, both short-term and long-term efficacy of pirfenidone and nintedanib in fibrosing ILD, specifically in connective disease associate ILD would be emphatically concerned by pulmonologists.

1. Introduction

Interstitial lung disease (ILD) is a cluster of diseases involved in the pulmonary parenchyma, with complex pathogenesis and heterogeneities, and reclassification of ILD gained academic concerning in 2002 [1–4]. The incidence and prevalence of ILD are growing gradually. Data from China demonstrated the newly diagnosed cases with ILD (per year) varied from 10 to 532 (2000–2012) [5]. Idiopathic pulmonary fibrosis (IPF) is the most common type of fibrosing ILD. In 2016, Raghu et al. presented the epidemiology of IPF in adults [6], showing the prevalence was twice times of itself ten years ago. Pulmonary fibrosis is the end-stage of ILD, which feature aberrant activation of fibroblasts and deposition of extracellular matrix. Advanced age is a vital risk factor for pulmonary fibrosis, whose incidence increases with age. With the aging population, researchers were full of enthusiasm about exploring every aspect from prevention, diagnosis, and clinical manifestations, to treatment, aiming to deepen the understanding of ILD.

Pirfenidone and nintedanib are the only two drugs approved for pulmonary fibrosis therapy lately [7]. Up to now, there are limited therapeutic advances in pulmonary fibrosis [8]. Lung transplantation is an effective solution for pulmonary fibrosis, but there are tremendous problems needed to be considered, such as the expensive cost, pulmonary infections after surgery, and rejection. The mean survival time of patients with ILD who received lung transplantation was 4.7 years [9]. The applications of pirfenidone and nintedanib succeeded in alleviating the impaired lung capacity [10–14], providing therapeutic anticipation against pulmonary fibrosis.

Bibliometric analysis of publication is an approach to reviewing research fields systemically using qualitative and quantitative methods [15]. Previous studies demonstrated that pirfenidone and nintedanib have significant abilities of anti-fibrotic effect and rescuing from declining lung function on IPF [16,17]. Pirfenidone and nintedanib have also been speculated to be effective pharmacotherapeutic options for other fibrosing ILD. Based on those exciting findings and reasonable hypotheses, scientists are trying to conduct more clinical trials or studies to expand the applications of pirfenidone and nintedanib. Therefore, we historically review the development features of the two drugs in fibrosing ILD through bibliometric, focus on bibliographical index information, draw scientific maps from aspects like the most productive countries, the leading contributory institutions, the influential scholars, the alteration of keywords, and so on. Moreover, we could provide some clues to hypothesize the possible trends of pirfenidone and nintedanib on the future lines of research.

2. Materials and methods

2.1. Data collection

We searched the Web of Science (WOS) Core Collection database for publications on pirfenidone or nintedanib in ILD. The retrieval time was February 24, 2024. All searches and downloads were performed within one day to avert biases originating from daily database updating. The search strategies were presented, as shown in Fig. 1. We confined the language to English and the article type to

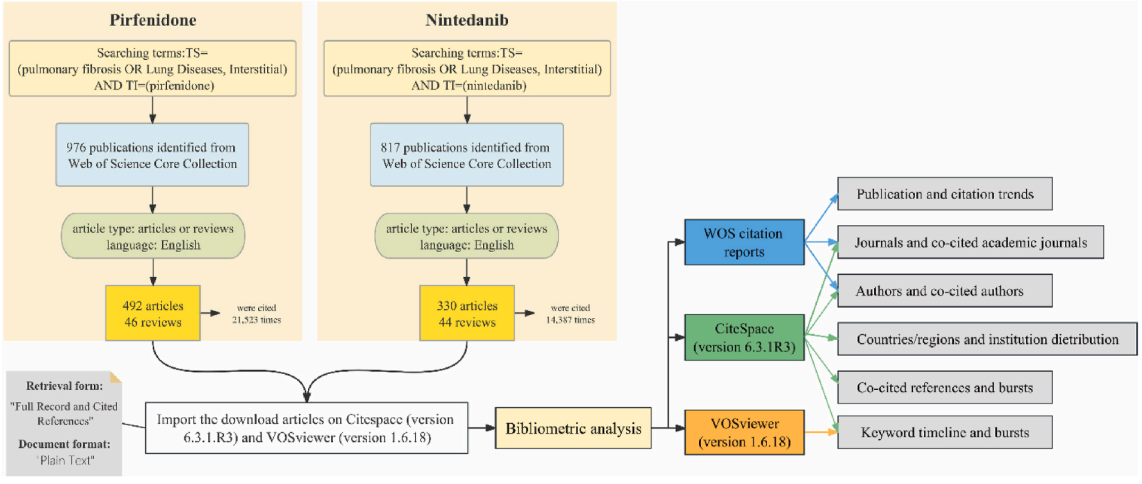

Fig. 1. Flow diagram of the included publications and methods of bibliometric analysis.

Review and Article. The election results of retrieval were exported in the form of "Full Record and Cited References", and saved as plain text files.

2.2. Bibliometric analyzing

The publication and citation trends were generated from the citation reports of WOS, using Microsoft Office Excel 2010. Using CiteSpace and VOSviewer for bibliometric analysis reference to software guidelines and published articles [18,19]. CiteSpace was adopted to quantify and qualify knowledge map, including countries/regions distribution, journals and co-cited academic journals,

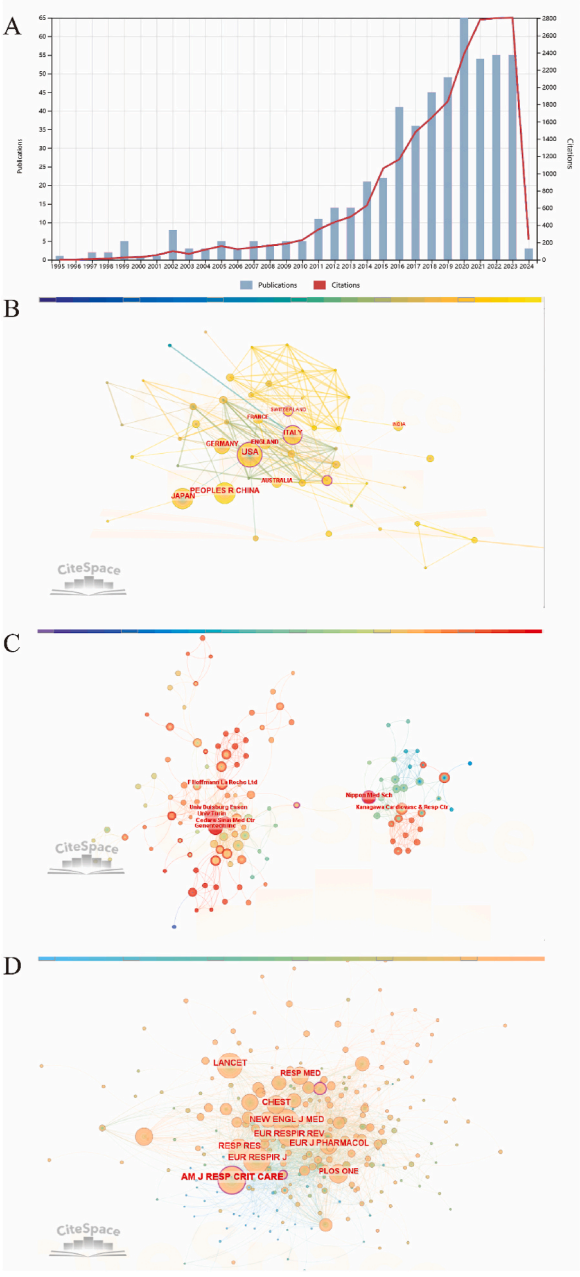

Fig. 2. Distribution of publications and citations about pirfenidone in ILD from different years, countries, institutions, and co-cited journals. (A) The chronological trend of publications about pirfenidone in ILD. (B) Distributions of publications about pirfenidone in ILD from different countries (C) Distributions of publications about pirfenidone in ILD from different institutions. (D) Co-cited journals of pirfenidone in ILD. Notes: The size of the node represents the co-occurrence frequencies while the links reflect the co-occurrence relationships. The color of the node and line indicates different years.

authors and co-cited authors, keyword bursts and their evolution, and co-cited references [20]. VOSviewer was used to map and visualize the network of keywords related to pirfenidone and nintedanib on the ILD [21]. Keywords were categorized according to co-occurrence analysis, and it produced varying clusters. Detailed steps of our study are illustrated in Fig. 1.

3. Results

3.1. The role of pirfenidone in ILD

3.1.1. The publication and citation trends of pirfenidone

The quantitative change of publications revealed the rise and fall of a research field to a certain degree. The number of annual publications about pirfenidone in ILD was demonstrated in Fig. 2A. Reclassification of ILD on 2002 attracted more attention from pulmonologists and researchers. During 1995–2010, the situation that less than 10 publications per year continued. Growth of publications started to crop up in 2011, and there was a sharp increase after 2015 with a peak of 65 entries in one year. In the last two years, the growth trend shrunk mildly. Hence, this evidence showed that some vital breakthroughs were achieved with pirfenidone in ILD over the past 15 years.

3.1.2. Leading countries/regions and institutions of pirfenidone

Publications acquired from 1995 to 2024 were analyzed over a one-year time slicing on Citespace. They were published by a total of 279 institutions from 58 countries/regions globally. The top 10 countries/regions dedicating themselves to pirfenidone in ILD were presented in Table 1. Considering the count of publications, the United States took first place (130, 16.15%), followed by China (102, 12.67%), Japan (101, 12.55%), Italy (66, 8.20%), Germany (52, 6.46%), and England (38, 4.72%). As shown in Fig. 2B, the leading countries were mapped out in a network, and the three largest nodes corresponded with the United States, China, and Japan. The United States and Italy had a centrality far beyond other countries, suggesting they may serve as an important part of this field.

Concerning productive institutions, the top 10 institutions dedicating themselves to this research field were demonstrated in Table 1. Arranging the frequency of occurrence, we saw that Genentech Inc (15, 2.25%) and University of Turin (14, 2.10%) had built up a lead, followed by Nippon Medical School (13, 1.95%), Cedars Sinai Med Ctr (12, 1.80%), and Univ Calif Davis (12, 1.80%). A visual map of chief productive institutions was shown in Fig. 2C. The Nippon Medical School was surrounded by a purple circle, representing the institution that may have made a difference in this field.

3.1.3. Leading journals and Co-cited journals of pirfenidone

The major journals with the most publications about pirfenidone in ILD and most citations were explored. Overall, 277 sorts of academic journals published articles and reviews about pirfenidone in ILD. As shown in Table 2, we observed that scientific achievements of pirfenidone in ILD had a favored acceptance in these journals including RESP RES (n = 20), BMC PULM MED (n = 12), and EUR RESPIR J (n = 12), etc. These top journals played a stronger role in unsealing the promising therapeutic role of ILD.

As regards the co-cited analysis of journals, the results of the most frequently cited journals in Table 2, exhibited that AM J RESP CRIT CARE (n = 408) was the most cited journal related to pirfenidone in ILD. Moreover, other journals also exerted crucial effects on this field, such as EUR RESPIR J (n = 345), NEW ENGL J MED (n = 331), LANCET (287), EUR RESPIR REV (n = 212), RESP RES (n = 200), CHEST (n = 191), EUR J PHARMACOL (n = 188), PLOS ONE (n = 162), and RESP MED (n = 137), etc. The visual network showed that the source co-cited studies about pirfenidone in ILD were principally published in respiratory or pharmacological journals, as shown in Fig. 2D.

3.1.4. Leading authors and Co-cited authors of pirfenidone

To observe the most influential researchers who dedicated themselves to studying pirfenidone in ILD, we statistically analyzed the frequency of productive authors and co-cited authors. A total of 4359 authors applied themselves to the study of pirfenidone in ILD. As shown in Table 3, the top predominant scientists were Albera C from the University of Turin, Italy (n = 14), following researchers including Costabel U from Germany (n = 13), Noble PW (n = 11) and Azuma A (n = 11) from the United States, and Kreuter M from Germany (n = 10). From the table, we noticed that scientists who wield a lot of influence in this research field primarily came from the

Table 1
Distribution of pirfenidone-related publications from different countries/regions and institutions.

Rank	Country	N (%)	Centrality	Year	Institution	N (%)	Centrality	Year
1	USA	130 (16.15%)	0.36	1995	Genentech Inc	15 (2.25%)	0	2017
2	PEOPLES R CHINA	102 (12.67%)	0.01	2005	Univ Turin	14 (2.10%)	0.08	2014
3	JAPAN	101 (12.55%)	0.06	2002	Nippon Med Sch	13 (1.95%)	0.15	2010
4	ITALY	66 (8.20%)	0.28	2009	Cedars Sinai Med Ctr	12 (1.80%)	0.01	2014
5	GERMANY	52 (6.46%)	0.09	2011	Univ Calif Davis	12 (1.80%)	0	1998
6	ENGLAND	38 (4.72%)	0.06	2010	Univ Duisburg Essen	11 (1.65%)	0.09	2014
7	SOUTH KOREA	30 (3.73%)	0	2010	F Hoffmann La Roche Ltd	11 (1.65%)	0.06	2017
8	FRANCE	24 (2.98%)	0.01	2001	Marnac Inc	11 (1.65%)	0	1998
9	AUSTRALIA	23 (2.86%)	0.08	2014	Kanagawa Cardiovasc & Resp Ctr	10 (1.50%)	0.02	2010
10	SWITZERLAND	21 (2.61%)	0.15	2016	Shionogi & Co Ltd	9 (1.35%)	0.01	2002

Table 2
The top 10 journals and co-cited journals associated with pirfenidone in ILD.

Rank	Journal	Count	JCR (2022)	Co-cited Journal	Citation	JCR (2022)
1	RESP RES	20	Q1	AM J RESP CRIT CARE	408	Q1
2	BMC PULM MED	12	Q3	EUR RESPIR J	345	Q1
3	EUR RESP J	12	Q1	NEW ENGL J MED	331	Q1
4	ADV THER	11	Q2	LANCET	287	Q1
5	PULM PHARMACOL THER	11	Q3	EUR RESPIR REV	212	Q1
6	SARCOIDOSIS VASC DIF	11	Q4	RESP RES	200	Q1
7	EUR J PHARMACOL	10	Q1	CHEST	191	Q1
8	FRONT PHARMACOL	10	Q1	EUR J PHARMACOL	188	Q1
9	PLOS ONE	10	Q2	PLOS ONE	162	Q2
10	RESP MED	10	Q2	RESP MED	137	Q2

Table 3
The top 10 authors and co-cited authors associated with pirfenidone in ILD.

Rank	Author	Country	Count	Co-cited author	Country	Citation
1	Albera C	Italy	14	Raghu G	United States	326
2	Costabel U	Germany	13	King TE	United States	268
3	Noble PW	United States	11	Noble PW	United States	255
4	Azuma A	United States	11	Taniguchi H	Japan	173
5	Kreuter M	Germany	10	Richeldi L	Italy	161
6	Nathan SD	United States	9	Iyer SN	Canada	160
7	Margolin SB	United States	9	Azuma A	United States	149
8	Kirchgaessler KU	Switzerland	9	Oku H	Japan	125
9	Giri SN	United States	9	Ley B	United States	95
10	Behr J	Germany	8	Nathan SD	United States	94

United States. Special experts and academic staff from European countries and the United States may function as vital players in the advances of studies about pirfenidone in ILD. Besides, scientists from Asia also played a key role in this field, not only providing evidence to fill in some absent epidemiology and curative effect of pirfenidone in ILD but also increasing awareness of pirfenidone and ILD in Asia [5,22,23].

As for the co-cited author analysis, Table 3 displayed the top 10 frequently cited authors. We noticed that Raghu G from the United States ranked first (n = 362), followed by King TE from the United States (n = 268), Noble PW from the United States (n = 255), Taniguchi H from Japan (n = 173), and RICHELDI L from Italy (n = 161), etc. Through their publications, we informed that their academic achievements significantly proved the momentous influence on which role of pirfenidone in ILD from administration dosage, safety, toxicity, side effects, and therapeutic efficiency.

3.1.5. Co-Occurring keywords and evolution of pirfenidone

Keywords are the major focal points of studies, illustrating the most emphasized issues and urgent needs in the real world. And the trend of keywords indicates the development and evolution of the specific field. The keywords of publications related to pirfenidone in ILD were clustered with VOSviewer and the burst of keywords from 1995 to 2024 was evaluated by Citespace. From Fig. 3A, we saw that there were two major clusters with different colors. The green cluster was inclined to molecules and mechanisms, including lung fibrosis, pathway, cell, administration, rat, mouse, vitro, collagen, etc. The red cluster is closely related to clinical trials, like vital capacity, safety, outcome, effectiveness, acute exacerbation, death, etc. The top 20 keywords of pirfenidone in ILD were shown in Supplementary Table S1. The burst of keywords with the year was presented in Fig. 3B. The considerable emerging keywords provided us a chance to review the history of pirfenidone in ILD. In retrospect, the keywords underwent a transition from a phase of preclinical research to clinical trials and large-scale real-world studies, even the comparative study of pirfenidone and nintedanib.

3.1.6. Co-cited references and burst references of pirfenidone

The epochmaking references were the landmarks associated with pirfenidone in ILD. To investigate the influential publication of pirfenidone in ILD, we adopted the characteristic co-cited references analysis on Citespace. As shown in Table 4, the top 10 co-cited references associated with pirfenidone in ILD were listed from 1995 to 2024. Of which articles and reviews were cited over 30 times. The two most cited studies reported remarkable effect of pirfenidone in patients with IPF concluded from three clinical trials, registered with the identifiers NCT01366209, NCT00287729, and NCT00287716 in ClinicalTrials.gov. ASCEND, CAPACITY 004, and CAPACITY 006 were their more known program name. Our statistical results reconfirmed the most representative reputation of them in this field. ASCEND solidified the beneficial effect of pirfenidone in patients with progressive IPF. Their results showed an approximately half reduction in FVC decline $\geq$10% in the pirfenidone treatment group, pirfenidone treatment resulted in no reduction in the 6-min walk test distance in IPF patients, also prolonged their progression-free survival [12]. The CAPACITY program (studies 004 and 006) confirmed that pirfenidone reduced deterioration in lung function (especially the forced vital capacity) in IPF. The third, fifth and eighth terms are the guideline or statements of IPF [11]. The high citation of them reflected that physician had attached

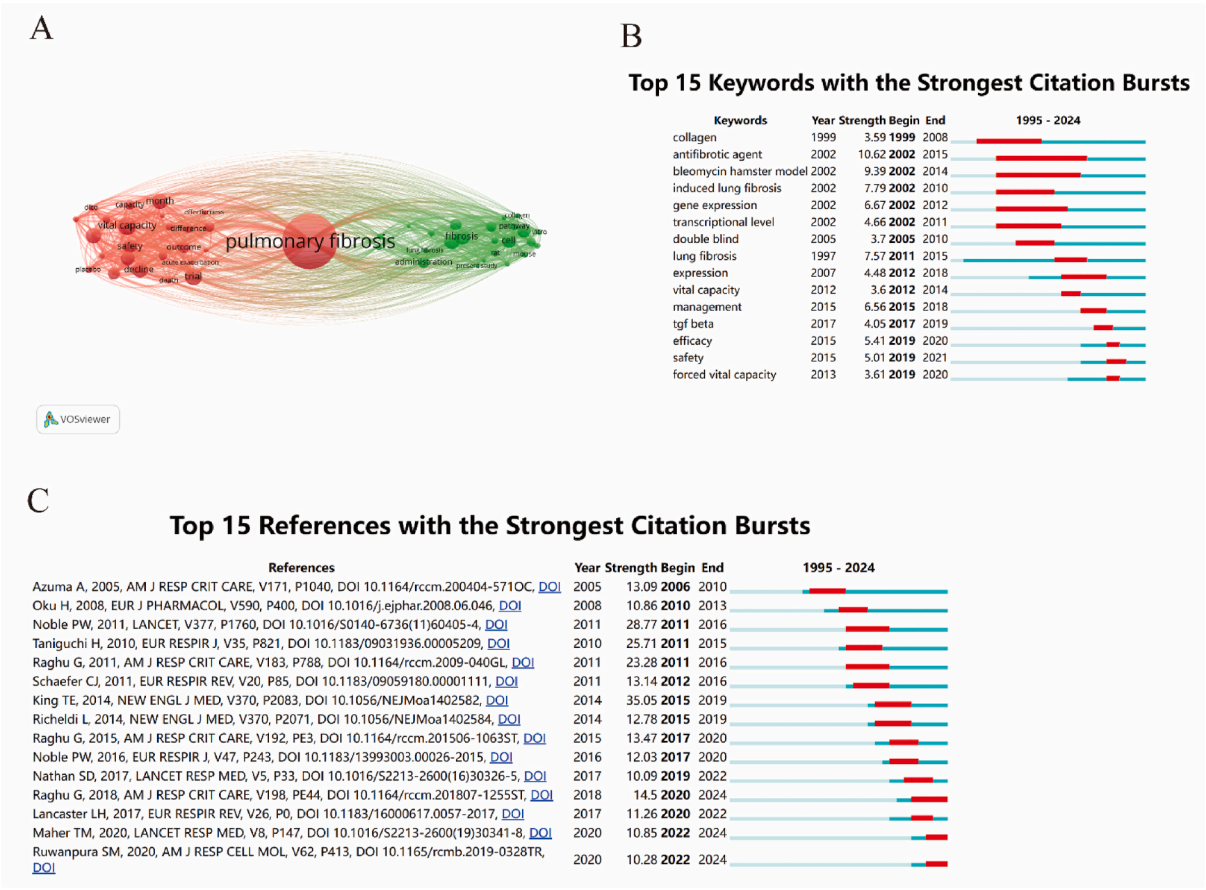

Fig. 3. The clusters and evolution of co-occurring keywords and references of pirfenidone in ILD. (A) The clusters of keywords about pirfenidone in ILD. (B) The burst timeline of keywords about pirfenidone in ILD. (C) The burst timeline of references about pirfenidone in ILD.

Table 4
The top 10 co-cited references associated with pirfenidone in ILD.

Rank	Citation	Author	Reference title	Journal	Year
1	127	King TE	A Phase 3 Trial of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis	NEW ENGL J MED	2014
2	71	Noble PW	Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials	LANCET	2011
3	58	Raghu G	An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management	AM J RESP CRIT CARE	2011
4	56	Noble PW	Pirfenidone for Idiopathic Pulmonary Fibrosis: Analysis of Pooled Data from Three Multinational Phase 3 Trials	EUR RESPIR J	2016
5	56	Raghu G	An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline	AM J RESP CRIT CARE	2015
6	51	Taniguchi H	Pirfenidone in idiopathic pulmonary fibrosis	EUR RESPIR J	2010
7	49	Richeldi L	Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis	NEW ENGL J MED	2014
8	43	Raghu G	Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline	AM J RESP CRIT CARE	2018
9	31	Schaefer CJ	Antifibrotic Activities of Pirfenidone in Animal Models	EUR RESPIR REV	2011
10	30	Conte E	Effect of Pirfenidone on Proliferation, TGF-β-induced Myofibroblast Differentiation and Fibrogenic Activity of Primary Human Lung Fibroblasts	EUR J PHARM SCI	2014

importance to the diagnosis, management, and therapy of lung fibrosis, represented by IPF. In addition, the other entries in the top 10 co-cited references also provided valuable advocation for the curative effect of pirfenidone in IPF, promoting the application of pirfenidone. The molecular target and mechanism involved in the antifibrotic effect of pirfenidone were also the hotspots in this field

[24]. Conte E et al. proved that pirfenidone modulates fibroblast proliferation and differentiation by attenuating TGF-β-induced pathways [25]. Lasting unmet need for exploring the underlying targets and signaling pathways of pulmonary fibrosis and anti-fibrotic drugs. Undoubtedly, all the scientific explorations are beneficial for deepening our understanding of pulmonary fibrosis and steering more novel therapeutical strategies.

Retrospectively, the burst map of highly cited references in Fig. 3C summarized the 15 most significant references of pirfenidone in pulmonary fibrosis. From them, we concluded that studies of pirfenidone in ILD had undergone a profound transition from 1995 to 2024. At begin, researchers focused on the antifibrotic effect of pirfenidone on animal models and early-stage clinical trials. After the stage of the phenotypic survey, the concern gradually moved to elaborated mechanisms of how pirfenidone work and its therapeutic performance on human. Subsequently, large-scale, phase-3 clinical trials of pirfenidone spring up in clinical from 2005, promoting the

Fig. 4. Distribution of publications and citations about nintedanib in ILD from different years, countries, institutions, and co-cited journals. (A) The chronological trend of publications about nintedanib in ILD. (B) Distributions of publications about nintedanib in ILD from different countries (C) Distributions of publications about nintedanib in ILD from different institutions. (D) Co-cited journals of nintedanib in ILD.

emergence of IPF-related guidelines and statements. Among the 15 studies, 3 publications belong to Raghu G, showing his tremendous contribution and influence on pirfenidone in ILD.

3.2. The role of nintedanib in ILD

3.2.1. The publication and citation trends of nintedanib

From 2012 to October 2024, a total of 374 publications involving the role of nintedanib in ILD were retrieved on WOS according to the search criteria, including 330 articles and 44 reviews. The total number of citations was 14,387 times, and the average number of citations per publication was 38.37 times. As shown in Fig. 4A, the totality of publications and citations both rises steadily and gradually year by year. The total number of publications increased maximally to 63 in 2021, and the number of citations reached a summit at 2941 in 2023. These data demonstrated that nintedanib is more and more commonly used to treat ILD over the last decade.

3.2.2. Leading countries/regions and institutions of nintedanib

A total of 238 institutions from 47 countries/regions co-authored 374 publications from 2012 to February 2024. As shown in Table 5, Japan with the highest sum of publications ranked first (111, 14.84%), followed by the United States (103, 13.77%), Germany (102, 13.64%), Italy (62, 8.29%), and England (53, 7.09%). As displayed in Fig. 4B, the size of the nodes represents the publication output of this country/region, while the thickness of the purple ring around the nodes indicates the value of centrality. Among the top 10 nations, the United States had higher centrality with 0.29, suggesting it exerted a crucial role in the cooperation between countries. Meanwhile, we concluded from Table 5 and Fig. 4C that the maximum number of publications was from Boehringer Ingelheim (99, 10.27%), followed by Imperial College London (31, 3.22%) and Nippon Medical School (27, 2.80%).

3.2.3. Leading journals and Co-cited journals of nintedanib

In total, the researchers have published papers about nintedanib in ILD in 174 academic journals. Table 6 presented the top 10 journals involving this field and RESP RES as the dominant journal that published the most papers (n = 16), followed by EUR RESP J and PULM PHARMACOL THER (n = 12). As for the co-cited journals in Table 6 and Fig. 4D, the journal New ENGL J MED (n = 330) ranked first, followed by EUR RESPIR J (n = 290), AM J RESP CRIT CARE (n = 274), RESP RES (n = 202), and LANCET RESP MED (n = 58). Moreover, according to the JCR in 2022 (Clarivate, United Kingdom), eight journals were in the Q1 JCR division.

3.2.4. Leading authors and Co-cited authors of nintedanib

A total of 3297 authors published papers related to the use of nintedanib to treat fibrosing ILD. As shown in Table 7, Stowasser S from Boehringer Ingelheim, Germany, had published the maximum number of publications (n = 36), followed by Richeldi L (n = 22), and Azuma A (n = 20). The authors from Japan and the Germany occupied half positions in the top 10. Therefore, concern for authors from Japan, Germany, and Italy roughly ensures we catch the dynamic forefront of nintedanib in fibrosing ILD.

Table 7 also presented the top 10 most frequently co-cited authors, including Richeldi L (n = 304), Raghu G (n = 209), and Wollin L (n = 203). Richeldi L from Universita Cattolica del Sacro Cuore Facolta di Medicina e Chirurgia, Roma, Italy, was the most co-cited and second most productive author, placing him among the top ten in both lists. Other authors ranked highly on both lists were Kolb M, Cottin V, and Wollin L. Richeldi L are mainly focused on early diagnosis, biomarkers, and therapeutic effects for ILD. Richeldi L also had been actively involved in designing and conducting adequate randomized controlled trials of nintedanib in IPF, particularly on the alternative of the proper clinical endpoints and the most appropriate statistical analyses.

3.2.5. 3.2.5 Co-Occurring keywords and evolution of nintedanib

As shown in Supplementary Table S2,the top 20 keywords were listed, among which “idiopathic pulmonary fibrosis”, “efficacy”, “safety”, and “tyrosine kinase inhibitor” appeared more than 60 times. Other following terms, including “acute exacerbation”, “survival”, “mortality”, and “systemic sclerosis”, indicated that the exploration of nintedanib in ILD had extended to observe long-term benefits or specific conditions of illness. In addition, Fig. 5A demonstrated a result of network cluster analysis on keywords with four different colors. The clusters of keywords showed emphases of this field. The green cluster was inclined to molecules and mechanisms, including tyrosine kinase inhibitor, expression, mouse, etc. The red cluster mainly consisted of safety, trial, adverse

Table 5
Distribution of nintedanib-related publications from different countries/regions and institutions.

Rank	Country	N (%)	Centrality	Year	Institution	N (%)	Centrality	Year
1	JAPAN	111 (14.84%)	0.08	2014	Boehringer Ingelheim	99 (10.27%)	0.07	2014
2	USA	103 (13.77%)	0.29	2014	Imperial College London	31 (3.22%)	0.05	2013
3	GERMANY	102 (13.64%)	0.08	2014	Nippon Medical School	27 (2.80%)	0.04	2014
4	ITALY	62 (8.29%)	0.21	2016	McMaster University	26 (2.70%)	0.14	2014
5	ENGLAND	53 (7.09%)	0.1	2013	Kanagawa Cardiovascular & Respiratory Center	23 (2.39%)	0.04	2015
6	FRANCE	48 (6.42%)	0.16	2014	University of Michigan	21 (2.18%)	0.04	2014
7	CANADA	35 (4.68%)	0.11	2014	University of Michigan System	21 (2.18%)	0.04	2014
8	PEOPLES R CHINA	33 (4.41%)	0	2015	Catholic University of the Sacred Heart	19 (1.97%)	0.08	2017
9	SWITZERLAND	22 (2.94%)	0.14	2014	CHU Lyon	18 (1.87%)	0.04	2014
10	BELGIUM	19 (2.54%)	0.03	2015	IRCCS Policlinico Gemelli	18 (1.87%)	0.03	2017

Table 6
The top 10 journals and co-cited journals associated with nintedanib in ILD.

Rank	Journal	Count	JCR (2022)	Co-cited Journal	Citation	JCR (2022)
1	RESP RES	16	Q1	NEW ENGL J MED	330	Q1
2	EUR RESP J	12	Q1	EUR RESP J	290	Q1
3	PULM PHARMACOL THER	12	Q3	AM J RESP CRIT CARE	274	Q1
4	BMC PULM MED	11	Q3	RESP RES	202	Q1
5	RESPIRATION	9	Q2	LANCET RESP MED	158	Q1
6	SCI REP	9	Q2	RESP MED	146	Q2
7	ADV THER	8	Q2	CANCER RES	135	Q1
8	ERJ OPEN RES	8	Q2	J PHARMACOL EXP THER	131	Q2
9	RESPIR INVESTIG	8	Q2*	THORAX	130	Q1
10	RESP MED	7	Q2	LANCET	126	Q1

* Emerging Sources CitationIndex, which were without Journal Citation Reports (JCR) division but Journal Citation Indicator (JCI) division.

Table 7
The top 10 authors and co-cited authors associated with nintedanib in ILD.

Rank	Author	Country	Count	Co-cited author	Country	Citation
1	Stowasser S	Germany	36	Richeldi L	Italy	304
2	Richeldi L	Italy	22	Raghu G	United States	209
3	Azuma A	Japan	20	Wollin L	Germany	203
4	Kolb M	Canada	19	Hilberg F	Austria	132
5	Ogura T	Japan	18	King TE	United States	111
6	Cottin V	France	13	Flaherty KR	United States	110
7	Maher T	British	13	Distler O	Switzerland	87
8	Inoue Y	Japan	13	Cottin V	France	71
9	Schlenker-Herceg R	United States	13	Kolb M	Germany	70
10	Wollin L	Germany	12	Crestani B	France	68

event, forced vital capacity, acute exacerbation, progressive fibrosing interstit, etc. The yellow cluster focused on the systemic sclerosis (SSc) and SSc-ILD. Next, we used CiteSpace's burst detection function to determine the top 15 terms with the most citation bursts. As displayed in Fig. 5B, we saw that at the early stage, studies preferred to describe nintedanib with the name bibf 1120. And then studies stepped into the dose escalation and dose expansion stage. In the past five years, "systemic sclerosis", "pharmacokinetics", "mortality" and "subgroups" sprung up. New studies attempted to magnify the application of nintedanib and elaborate on the pharmacokinetic characteristics of nintedanib.

3.2.6. Co-cited references and burst references of nintedanib

The co-cited analysis of references listed the top 10 co-cited references associated with nintedanib in ILD in Table 8. The article titled "Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis" from Richeldi L, Italy had citations up to 112 times. This document was the vanguard of uncovering the exciting role of nintedanib in IPF. Another article named "Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS(®) trials", published by Richeldi L, appeared in the table. Again, these results restated the tremendous contribution of Richeldi L in studies of nintedanib. From 2016 to 2019, the most influential references of nintedanib in ILD concerned specified subgroups, systemic sclerosis-associated ILD, and even progressive fibrosing ILD [26–29]. The second and third items are about the roles of nintedanib for progressive fibrosing ILD and SSc-ILD, our findings sensitively present the major problems or the priorities during the development of nintedanib in fibrosing ILD. The fourth and sixth items, both belonging to Wollin L, explained the primary therapeutic mechanism of nintedanib. Conclusions from in vitro exhibited that nintedanib interferes with biological processes such as fibroblast proliferation, invasiveness and differentiation, the secretion of ECM, etc.

The burst map of references with the strongest citation was presented in Fig. 5C. Two blockbuster studies reported the powerful anti-fibrotic effect of nintedanib in IPF in 2011. They were the prologue to this field. Subsequently, further investigation focused on the pharmacokinetics and metabolism of nintedanib, as well as the safety, tolerability, and adverse effects. After exploring the pharmacological properties of nintedanib, this research field marched in rapid development. We learned of results on the efficacy and safety of nintedanib in patients with IPF and FVC of $\leq$50 % of predicted value, in patients with progressive pulmonary fibrosis, and a long-term follow-up, etc. The last publication listed in Fig. 5C, titled "Nintedanib in Progressive Fibrosing Interstitial Lung Diseases", provided a significant conclusion that nintedanib is effectual drug for a broad range of fibrosing lung diseases, and the adverse events of nintedanib were diarrhea. In the future, the application of nintedanib could expand to a special clinical manifestation, progressive fibrosing ILD, whether its different onsets.

4. Discussion

Pirfenidone and nintedanib are sort of orphan drugs for IPF, and they would continue to occupy this position in the foreseeable

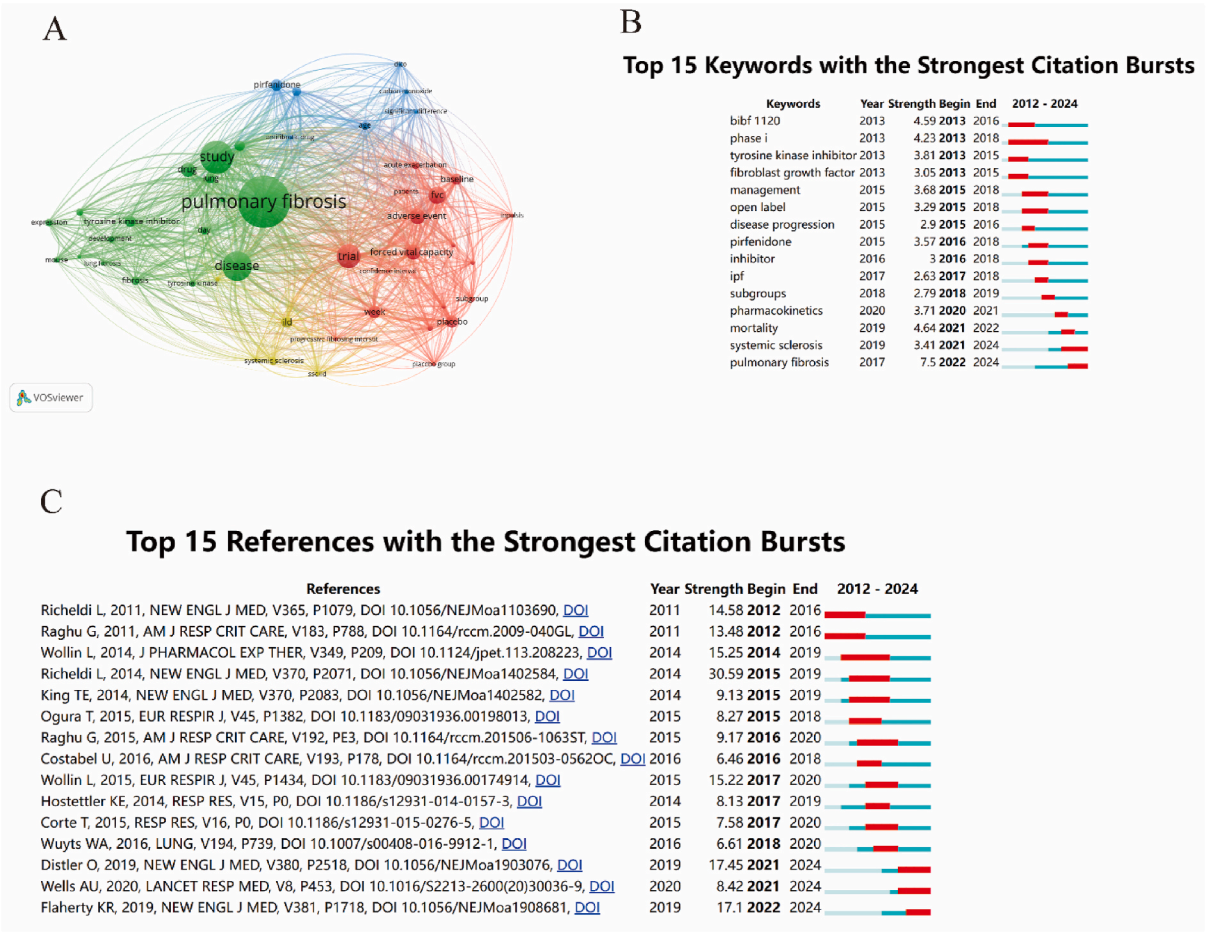

Fig. 5. The clusters and evolution of co-occurring keywords and references of nintedanib in ILD. (A) The clusters of keywords about nintedanib in ILD. (B) The burst timeline of keywords about nintedanib in ILD. (C) The burst timeline of references about nintedanib in ILD.

Table 8
The top 10 co-cited references associated with nintedanib in ILD.

Rank	Citation	Author	Reference title	Journal	Year
1	112	Richeldi L	Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis	NEW ENGL J MED	2014
2	81	Distler O	Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease	NEW ENGL J MED	2019
3	79	Flaherty KR	Nintedanib in Progressive Fibrosing Interstitial Lung Diseases	NEW ENGL J MED	2019
4	73	Wollin L	Mode of Action of Nintedanib in the Treatment of Idiopathic Pulmonary Fibrosis	EUR RESPIR J	2015
5	67	Raghu G	Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline	AM J RESP CRIT CARE	2018
6	61	Wollin L	Antifibrotic and Anti-inflammatory Activity of the Tyrosine Kinase Inhibitor Nintedanib in Experimental Models of Lung Fibrosis	J PHARMACOL EXP THER	2014
7	48	Crestani B	Long-term Safety and Tolerability of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis: Results from the Open-Label Extension Study, INPULSIS-ON	LANCET RESP MED	2019
8	45	Raghu G	An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline	AM J RESP CRIT CARE	2015
9	39	Costabel U	Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS	AM J RESP CRIT CARE	2016
10	37	Richeldi L	Nintedanib in Patients with Idiopathic Pulmonary Fibrosis: Combined Evidence from the TOMORROW and INPULSIS(®) trials	RESP MED	2016

future [30]. Our study retrospectively reviewed and summarized distinguishing features of pirfenidone and nintedanib in fibrosing ILD via bibliometric analysis. The studies of the two drugs in pulmonary diseases are in their infancy at present. Our results provided a framework to acquire the development history and rising edges of pirfenidone and nintedanib in respiratory diseases, especially in ILD,

especially pulmonary fibrosis.

Assessing articles and reviews associated with pirfenidone in ILD from seven aspects (citation trend, leading countries/regions, institutions, journals, authors, keywords, and references), we statistically summarized the features of papers about pirfenidone in ILD. Pirfenidone was first discovered by Marnac Inc in 1974 [31]. Scientists from Japan performed clinical trials to evaluate its underlying therapeutic effect on IPF. In 2008, pirfenidone, under the trade name pirespa, was approved for IPF in Japan [32]. In 2014, pirfenidone, under the trade name Esbriet from Genetech Inc, was approved for IPF in America. Since then, the publication number stepped into a rapid increase stage, and the growth has gone to today. The United States, Japan, China, and Italy had exerted insightful effects on the role of pirfenidone in ILD, considering the paper counts and high citations. The journal of RESP RES published papers about pirfenidone in fibrosing ILD with the most frequency. Authors with top citations were mainly from the United States, counting half of the top 10 co-cited authors. The five authors (Raghu G, King TE, Noble PW, Azuma A, Nathan SD) contributed to this research field by conducting high-quality randomized controlled trials of pirfenidone in IPF, and their work facilitated the development and application of pirfenidone in the respiratory system, basically as the milestones of this field [7,33–53]. As for the co-occurrence keywords map of pirfenidone, we noticed that the clinical-related and molecular pathway-related keywords occupied more than half area of the picture. Attention to the efficacy and safety of pirfenidone in clinical trials was a priority for physicians. Most side effects of pirfenidone were reported with photoallergic reaction, gastrointestinal reaction, dysfunction of the liver, etc [53]. But the adverse effect is controllable overall. New clinical trials are performed to investigate the inhaled delivery of pirfenidone in IPF [54,55]. Inspiring results from these afoot controlled trials are hopeful to support a novel delivery method of pirfenidone in IPF and other ILD.

Nintedanib, a triple angiokinase inhibitor, was designed by Boehringer-Ingelheim for anti-angiogenesis initially. We described the productive and influential countries/regions, journals, and authors of nintedanib in ILD, and found the keywords and burst references, to draw the academic transitions of nintedanib in ILD. Compared to pirfenidone, a shorter time boxing of enrolled publications, nearly twelve years, showed the emerging anti-fibrotic role of nintedanib in IPF and ILD. And there are plenty of opportunities to elaborately analyze the underlying characteristics of nintedanib. Japan, Germany, the United States, and Italy were the productive and significant countries in discovering the function of nintedanib in ILD, primarily in IPF. The top three scientists with the most citations (Richeldi L from Italy, Raghu G from the United States, and Wollin L from Germany), are leading the evolution of studies about nintedanib in pulmonary fibrosis. The most influential papers on nintedanib in pulmonary fibrosis were published in New ENGL J MED, EUR RESPIR J, and AM J RESP CRIT CARE. These journals are typically outstanding journals on respiratory systems. Recently, Richeldi L et al. reported an original finding of preferential phosphodiesterase 4B inhibitor for IPF in New ENGL J MED [56]. The network of keywords showed the most concerning spheres of nintedanib involved in the therapeutic effects, end-points, subtypes of diseases, and adverse effects. Efficacy and safety of nintedanib are the aspects with the most interest when we stay at boom years. The common side effects of nintedanib were diarrhea, nausea, and impaired functions of the liver etc [14,57]. Nintedanib for children and adolescents with fibrosing ILD is in progress [58,59]. New practice and progress with nintedanib in the pulmonary arterial hypertension model showed a positive curative effect to prevent the impaired function and structure of pulmonary arteries [60,61]. All these advances of nintedanib in respiratory diseases convinced us that nintedanib is capable to establish its reputation on diverse pulmonary diseases by powerful anti-fibrosis, anti-inflammation, and anti-angiogenesis. Additionally, the combination of pirfenidone and nintedanib in pulmonary fibrosis is the burgeoning research orientation [62–64]. There are disparities between the targets and molecular pathways of pirfenidone and nintedanib [65]. The two drugs were found to prevent the worsening forced vital capacity, but they failed to reverse or improve the lung capacity. The combination of pirfenidone and nintedanib for fibrosing ILD may result in a more intriguing therapeutic effect.

There are some limitations in our study. Bibliometric is naturally bibliographic index-based secondary analysis, and is insufficient for newly publications with deficient and inadequate index. Although our results showed the most cited and significant publications and bursts of keywords over time, our study only summarized the most capital and prevailing characteristics during development, and provide a rough orbit about the evolvement of pirfenidone and nintedanib in fibrosing ILD. Our findings measurably revealed a three decades growth of pirfenidone and nintedanib in ILD. Keeping with the most influential scholars, the most productive institutions, and the most reputative journals are benefit for pulmonologists and researchers updating professional knowledge. Our results showed that the predominating keywords of pirfenidone and nintedanib in fibrosing ILD focus on evaluation, efficacy, safety, mechanism, etc. In the future, the diversified, quantifiable, holistic assessments of pulmonary fibrosis are demanding for pulmonologists. Moreover, cohort studies about pirfenidone and nintedanib in different patient populations, for example, patients with progressive pulmonary fibrosis, with combined pulmonary fibrosis and emphysema, or pulmonary fibrosis with post viral infection, are significant for instructing applications of pirfenidone and nintedanib. Considering the unclear nosogenesis and heterogeneity of pulmonary fibrosis, scientific exploration of biological mechanisms is one of the primary approaches to invent novel pharmacological agents on pulmonary fibrosis.

5. Conclusion

We are currently in a sharp upsurge of studies about pirfenidone and nintedanib in pulmonary fibrosis. The United States and Europe played crucial roles in the development of the two drugs in ILD. Papers published in NEW ENGL J MED, AM J RESP CRIT CARE, and EUR RESPIR J had a profound influence on pulmonary-related advances of pirfenidone and nintedanib. Despite the disparate targets and molecular pathways of the two anti-fibrotic agents, we observed a similar evolution of studies about the two drugs after 2014. Based on the confirmative anti-fibrotic effect of pirfenidone and nintedanib for IPF, further studies about them are trying to extend the application to systemic sclerosis, and even other connective tissue disease-associated interstitial lung diseases. Moreover, the efficacy of the two drugs in subgroups, particularly progressive pulmonary fibrosis, gradually becomes the academic hotspots of

pirfenidone and nintedanib. Therapeutic expectations for pirfenidone and nintedanib in more illness conditions worth continuing attention.

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Data availability statement

Not Applicable.

CRediT authorship contribution statement

Jia Liu: Writing – original draft, Visualization, Software, Methodology, Investigation, Data curation, Conceptualization. **Faping Wang:** Writing – review & editing, Supervision. **Yiwen Hong:** Writing – review & editing, Validation, Investigation. **Fengming Luo:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

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Appendix A. Supplementary data

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