Original Article

Global research hotspots and research trends on idiopathic pulmonary fibrosis: a bibliometric and visualization analysis

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Background: Idiopathic pulmonary fibrosis (IPF) is a life-threatening disease, the progression of which current drug therapy cannot reverse. This study analyzed current research hotspots and future research trends in IPF through bibliometric methods, with the aim of providing a reference for new therapeutic strategies.

Methods: Publications on IPF obtained from the Web of Science Core Collection database, The Literature Metrology Online Analysis Platform, and CiteSpace were used to analyze publication characteristics. VOSviewer was used to conduct keywords co-occurrence analysis and analyze research hotspots.

Results: A total of 7,016 publications related to IPF were identified from 2011 to 2020. The most contributions were from the USA and the five research institutions with the largest number of publications were all from that country. The *American Journal of Respiratory and Critical Care Medicine* was the most cited journal and had an incontrovertible academic impact with five of the top 10 high-cited references published in this journal. G Raghu was the academic authority in this domain in terms of both the number of publications and the most citations. By analyzing keywords, we identified three IPF research hotspot clusters, which are "clinical research", "pathogenesis research" and "diagnosis research" respectively.

Conclusions: We evaluated all publications concerning IPF research in the past decade through bibliometric analysis. The current research hotspot in this field is drug therapy for the condition using nintedanib and pirfenidone. Future research will focus on conducting multi-center randomized controlled trials to explore and evaluate new therapeutic drugs for IPF. It is hoped that this study can provide information and data support for further research and the development of new therapeutic drugs.

Keywords: Bibliometric analysis; hotspots; idiopathic pulmonary fibrosis (IPF); nintedanib; pirfenidone

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia of unknown etiology (1), and is one of the most common idiopathic interstitial pneumonia seen clinically. Although previously considered rare, its morbidity has shown an upward trend in recent years (2). The main manifestations are dry cough, and progressive and aggravated dyspnea, accompanied by restricted ventilation dysfunction and gas exchange dysfunction (3), which lead to hypoxia and even respiratory failure. Its chest high-resolution

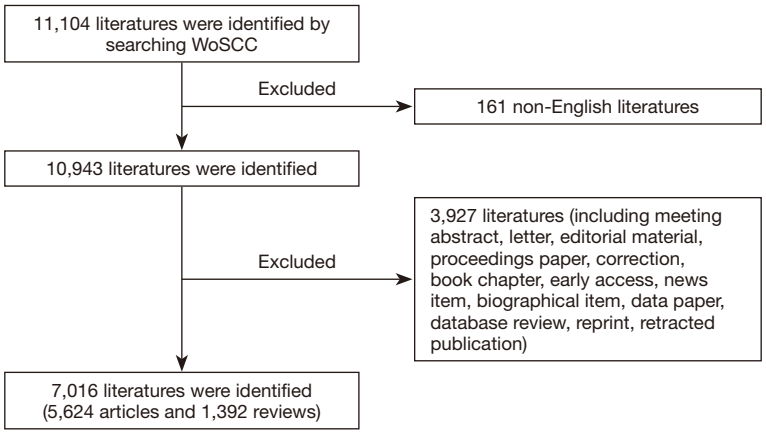

Figure 1 Flow chart of literature screening.

CT (HRCT) is characterized by subpleural and basal predominant honeycombing, with or without peripheral traction bronchiectasis (1). IPF has a poor prognosis, with a median survival time of only 3–5 years after diagnosis (4), although some patients may experience acute deterioration of respiratory function in a short period of time leading to death.

As the pathogenesis of IPF is unclear, and drug therapy cannot reverse the progression of the disease, most patients continue to deteriorate, and their quality of life is seriously reduced, causing a serious economic burden to patients, their families and communities. For these reasons, determining the pathogenesis of IPF and mechanisms by which the disease can be treated is crucial.

Bibliometrics is a discipline that uses mathematical and statistical methods to quantitatively analyze information (5). It can be used to assess the contributions of countries, institutions, journals, and authors to a particular research topic, and can determine research hotspots and forecast research trends in a certain field. While information gleaned from bibliometrics can also provide the basis for the formulation of clinical guidelines (6,7), there is currently no bibliometric study on IPF. The aim of this study was to analyze literature about IPF through information visualization software, and intuitively showed the importance of countries, institutions, authors and keywords in the network visualization map, thus summarize the current academic authority and achievements, identify hotspots and future directions, and provide a reference for future investigations.

Methods

Data collection

We performed an online search of the Web of Science Core Collection database on March 1, 2021. The search formula was set to TS = (idiopathic pulmonary fibrosis), time span = (2011–2020), and language = English. Only articles and reviews were selected (*Figure 1*) and the title, abstract, keywords, "country", "institution", "authors", "journal", and "references" were collected.

Data analysis

The Literature Metrology Online Analysis Platform (https://bibliometric.com/), CiteSpace v.5.7.R5(64-bit)W, and VOSviewer were used to perform bibliometric analysis, and the annual publication numbers were determined through the Literature Metrology Online Analysis Platform. CiteSpace is an optimal method for collaborative network analysis of productive countries, institutions, and authors, and can also be used for cited journals, cited references, and cited authors analysis. CiteSpace was used for keywords burst detection to trace research hotspots and research trends, and to perform "time slicing" function, by setting the "years per slice" to "1", and the "top N" to "50", to obtain the top 50 publications in a year in a single file. In this study, the node size represents the number of publications or the frequency of being cited. Centrality is an index to measure the importance of nodes in a network. A higher centrality indicates that a node is more important

in the network, and the purple rings outside the circle refer to high centrality. In CiteSpace, the timeline is displayed above the network visualization map, and the different link colors represent the different times. VOSviewer can classify keywords into different clusters according to co-occurrence analysis, and the different colors represent different clusters.

Results

In total, 7,016 publications (including 5,624 articles and 1,392 reviews) met the inclusion criteria from 2011 to 2020 (*Figure 1*). *Figure 2* shows the total number of publications annually, where the number of papers in IPF research maintained a gradual increasing trend from 2011 to 2020.

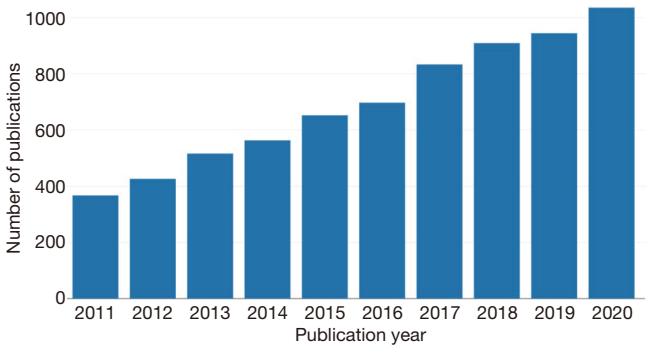

Figure 2 Number of annual publications.

Analysis of leading countries and institutions

The country collaboration network of IPF research is shown in *Figure 3*, and the top 10 countries contributing to it are shown in *Table 1*. The USA contributed the most publications [2,126], followed by Japan [898], China [833], England [539], and Germany [484]. Centrality is an index to measure the importance of nodes in a network, and it was apparent that the USA (centrality =0.2) was at the heart of the network, followed by Germany (centrality =0.18), and Japan (centrality =0.12). A higher centrality in a collaboration network means more frequent cooperation.

The institution cooperation network is visualized in *Figure 4*, which shows the top 10 institutions as including the University of Michigan [193], National Jewish Health [181], University of California, San Francisco [175], Mayo clinic [163], and University of Pittsburgh [160] (*Table 1*), which are all located in the USA. Among them, the highest ranking of centrality were the University of California, San Francisco (centrality =0.15) and National Jewish Health (centrality =0.12), respectively.

Analysis of cited journals and cited references

Table 2 lists the top 10 cited journals. The highest cited journal was the *American Journal of Respiratory and Critical Care Medicine*, which was cited 4,787 times, followed by the *European Respiratory Journal* [3,415] and *Chest* [3,086]. According to the 2019 standard of the JCR, seven journals

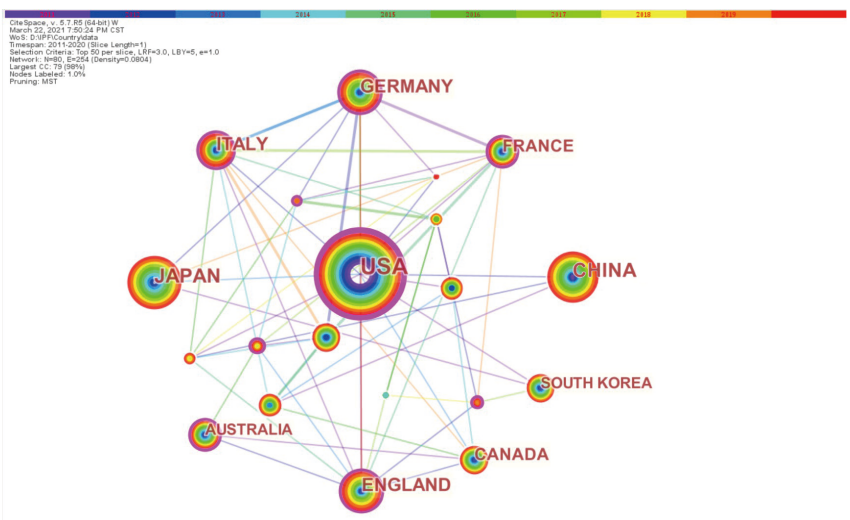

Figure 3 Cooperation network of the productive countries. The node size represents the number of publications of the country. The purple rings outside the circle refer to high centrality.

Table 1 Top 10 countries and institutions contributing to publications

Rank	Countries			Institutions		
	Countries	Article counts	Centrality	Institutions	Article counts	Centrality
1	USA	2,126	0.2	Univ Michigan	193	0.05
2	Japan	898	0.12	Natl Jewish Hlth	181	0.12
3	China	833	0.06	Univ Calif San Francisco	175	0.15
4	England	539	0.1	Mayo Clin	163	0.08
5	Germany	484	0.18	Univ Pittsburgh	160	0.09
6	Italy	434	0.12	Royal Brompton Hosp	142	0.11
7	France	302	0.11	Univ Washington	129	0.08
8	Canada	292	0.12	Univ Colorado	112	0.05
9	South Korea	233	0.06	Vanderbilt Univ	110	0.11
10	Australia	193	0.1	Univ Chicago	106	0.08

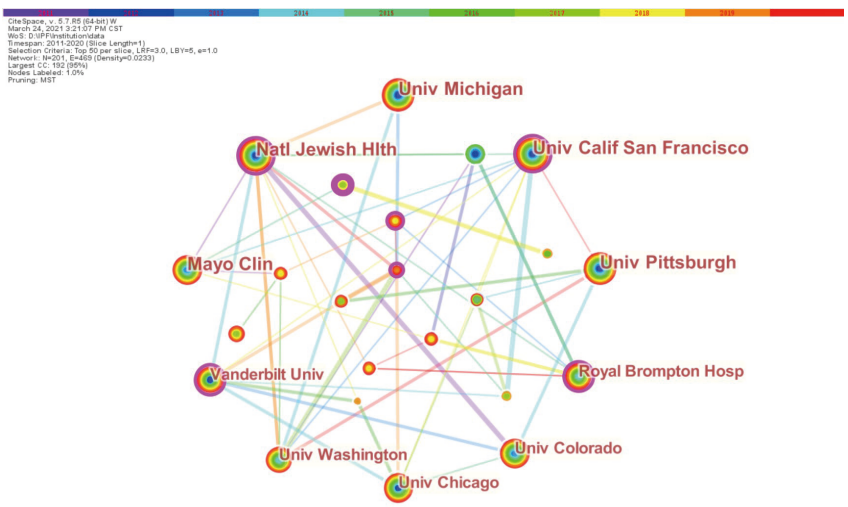

Figure 4 Cooperation network of the productive institutions. The node size represents the number of publications of the institution.

were sorted to Q1, and three were sorted to Q2. *The New England Journal of Medicine* had the highest impact factor (74.699), followed by the *American Journal of Respiratory and Critical Care Medicine* (17.452), and the *European Respiratory Journal* (12.339).

Details of the top 10 cited references are provided in *Table 3*. The publication titled "*An official ATS/ERS/JRS/ALAT statement*: *idiopathic pulmonary fibrosis*: *evidence-based guidelines for diagnosis and management*" was the most cited, being cited 913 times. The second most cited was "*Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis*", being cited 620 times, and "*A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis*" was the third (604 times). In the top 10 cited references, five publications were from the *American Journal of Respiratory and Critical Care Medicine*, three were from *The New England Journal of Medicine*, and two were from the *Lancet*.

Analysis of authors and co-cited authors

The author collaboration network of IPF is shown in *Figure 5*. The top 10 authors with the most publications include Wells AU [115], Maher TM [96], Raghu G [93], Collard HR [86], and Brown KK [84] (*Table 4*).

Table 2 Top 10 cited journals

Rank	Cited journals	Cited counts	JCR [2019]	IF [2019]
1	*American Journal of Respiratory and Critical Care Medicine*	4,787	Q1	17.452
2	*European Respiratory Journal*	3,415	Q1	12.339
3	*Chest*	3,086	Q1	8.308
4	*The New England Journal of Medicine*	2,595	Q1	74.699
5	*Thorax*	2,344	Q1	10.844
6	*PLoS One*	2,229	Q2	2.740
7	*American Journal of Respiratory Cell and Molecular Biology*	2,040	Q1	5.373
8	*American Journal of Physiology-Lung Cellular and Molecular Physiology*	1,872	Q2	4.418
9	*Journal of Clinical Investigation*	1,764	Q1	11.864
10	*Respiratory Medicine*	1,762	Q2	3.095

Table 3 Top 10 cited references

Rank	Title	Journal	Publication year	Corresponding author	Cited counts
1	An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management	*American Journal of Respiratory and Critical Care Medicine*	2011	Raghu G	913
2	Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis	*The New England Journal of Medicine*	2014	Richeldi L	620
3	A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis	*The New England Journal of Medicine*	2014	King TE	604
4	An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. an update of the 2011 clinical practice guideline	*American Journal of Respiratory and Critical Care Medicine*	2015	Raghu G	367
5	An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias	*American Journal of Respiratory and Critical Care Medicine*	2013	Travis WD	349
6	Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline	*American Journal of Respiratory and Critical Care Medicine*	2018	Raghu G	296
7	Idiopathic pulmonary fibrosis	*Lancet*	2011	King TE	207
8	Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials	*Lancet*	2011	Noble PW	197
9	Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report	*American Journal of Respiratory and Critical Care Medicine*	2016	Collard HR	182
10	Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis	*The New England Journal of Medicine*	2012	Raghu G	164

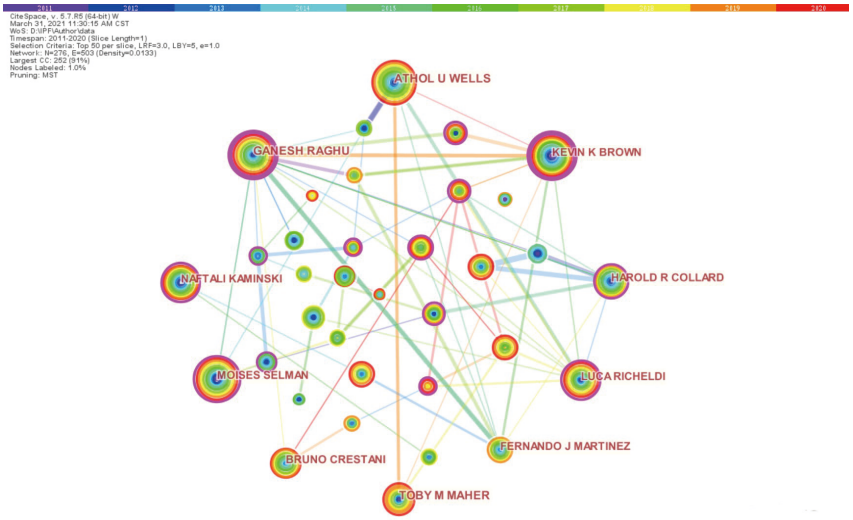

Figure 5 Cooperation network of the productive authors. The node size represents the number of papers published by the author. The link color represents the earliest date of their collaboration.

Table 4 Top 10 productive authors and co-cited authors contributing to publications

Rank	Authors	Article counts	Centrality	Co-cited authors	Cited counts
1	Wells AU	115	0.05	Raghu G	2,853
2	Maher TM	96	0.08	King TE	1,528
3	Raghu G	93	0.21	Richeldi L	1,024
4	Collard HR	86	0.14	Travis WD	820
5	Brown KK	84	0.2	Selman M	807
6	Selman M	81	0.11	Collard HR	750
7	Richeldi L	74	0.16	Ley B	710
8	Kaminski N	73	0.13	Noble PW	589
9	Martinez FJ	67	0.06	Flaherty KR	585
10	Crestani B	65	0.08	Wells AU	469

Among them, Raghu and Brown had high centrality and collaborated extensively with other authors, and although Wells and Maher published more papers, they had low centrality and less collaboration with other authors. *Figure 5* shows the earliest collaborations were in 2015 (the link is shown as light green).

Co-cited authors networks are visualized in *Figure 6*. Of the 10 most cited authors, Raghu ranks first, with 2,853 citations, followed by King [1,528], and Richeldi [1,024] (*Table 4*). The earliest link of Raghu is shown in purple (in 2011), while that of Richeldi is green (in 2016), implying he is more recent author.

Analysis of research hotspots and research trends

Keywords were identified in 7,016 documents and analysed by VOSviewer, and the network visualization map shows their frequency of occurrence (*Figure 7*). The analysis identified 217 keywords that appeared more than 218 times and divided them into three clusters: cluster 1 (clinical research, red); cluster 2 (pathogenesis research, green); cluster 3 (diagnosis research, blue). In cluster 1, the high-frequency keywords were "patient" [15,676], "IPF" [10,737], "idiopathic pulmonary fibrosis" [6,718], "study" [5,961], and "treatment" [4,142]. In cluster 2, the keywords that

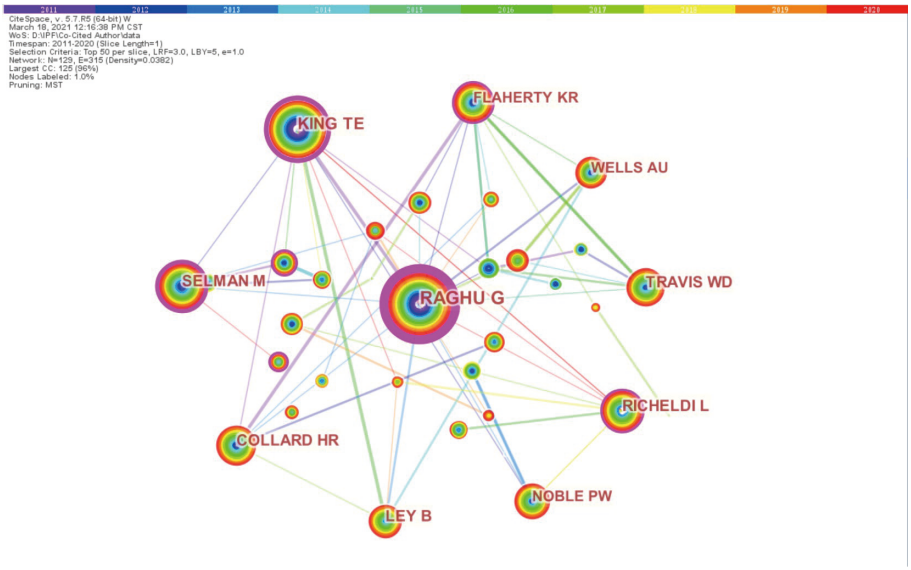

Figure 6 Cooperation network of the co-cited authors. The size of the node represents the frequency the author was cited. The link color represents the earliest time the author was co-cited.

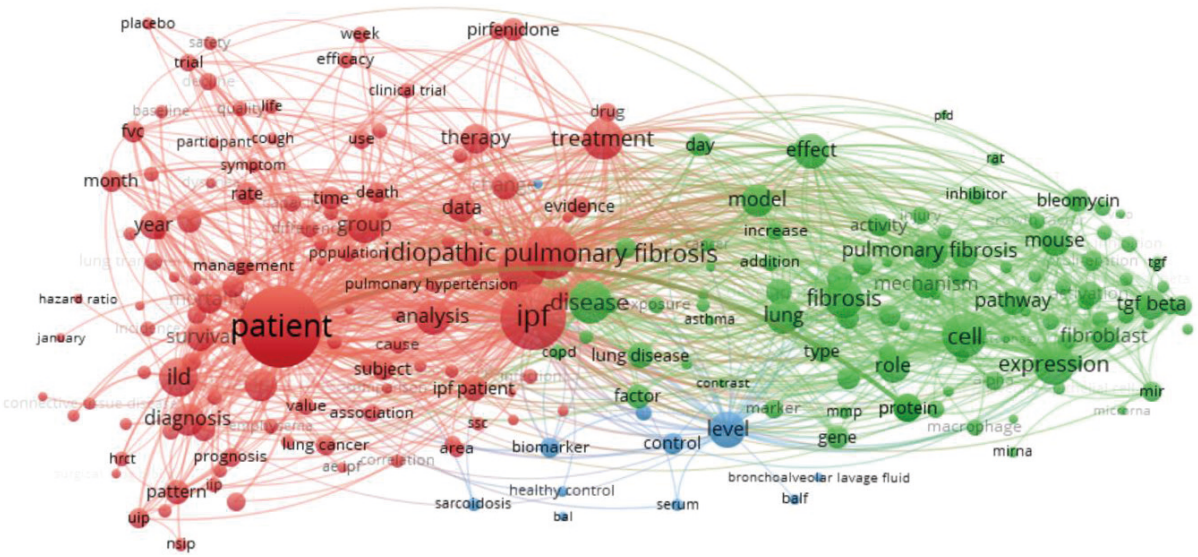

Figure 7 Network visualization map of keywords. The different colors represent the different clusters. Large circles indicate the keywords of high frequency.

appeared frequently were "cell" [4,908], "disease" [4,539], "expression" [4,204], "fibrosis" [3,775], and "pulmonary fibrosis" [3,136], and in cluster 3, the primary keywords were "level" [3,224], "control" [1,155], "biomarker" [998], "concentration" [707], and "sarcoidosis" [445]. Table S1 shows details of the keywords.

Figure 8 shows the top 25 keywords with the strongest citation bursts from 2011 to 2020 by CiteSpace, which was used to analyze the temporal trend of research hotspots shift.

Discussion

The incidence of IPF seems to be increasing in recent years. In this study, we applied information visualization

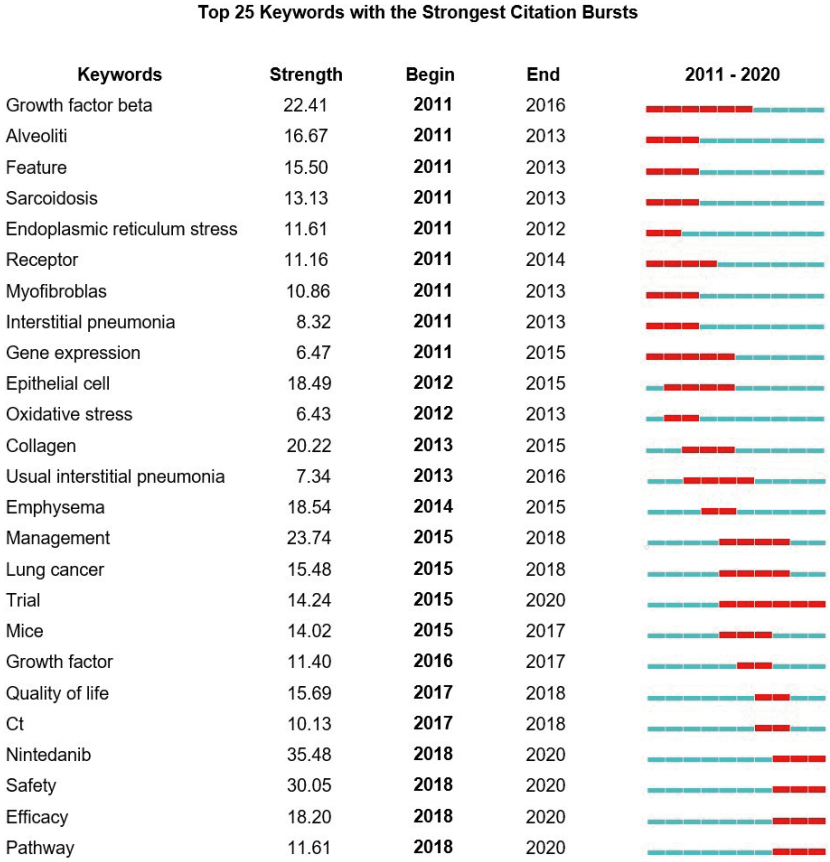

Figure 8 Top 25 keywords with the strongest citation bursts. Each short line represents 1 year. The short red line represents the year in which the keywords with the citation bursts. The short blue line represents other years.

software to analyze literature on IPF published from 2011 to 2020. The results showed the total number of annual global publications on IPF research maintained a gradual increasing trend in the past 10 years, indicating it is an increasingly important research field.

The USA had the largest number of publications and the highest centrality, and most frequently collaborated with other countries including Japan, China, England, and Germany. A strong research culture underpinned by significant public and private funding no doubt underpins this. China and South Korea also contributed many publications, but they were of low centrality and may demonstrate a lack of communication with other countries. We speculate that these countries should pay more attention to international cooperation, especially with advanced countries in this field, to promote their own progress in IPF research.

The top five institutions publishing research in the field of IPF were also from the USA, and while the University of California, San Francisco and National Jewish Health collaborated most with other institutions, which is worth learning by those seldom communicating with each other.

The *American Journal of Respiratory and Critical Care Medicine* was cited 4,787, making it the most cited publication. Five of the top 10 high-cited references were also published in this journal, which confirms its academic authority in the field of IPF research, reflected in its high impact factor of 17.452.

The publication attracting the highest number of citations concerned guidelines for IPF and was authored by Raghu *et al.* in 2011. The paper is an official statement issued by organizations including the American Thoracic Society and European Respiratory Society, is an international evidence-based guideline on the definition, epidemiology, diagnosis, and treatment of IPF, and is generally considered as the basis of IPF research (8).

The second highest cited publication concerned a phase 3 trial investigating the efficacy and safety of nintedanib in

IPF published in *The New England Journal of Medicine* in 2014 and authored by Richeldi *et al.* The research proved that 150 mg of nintedanib twice daily could significantly reduce the decline of forced vital capacity (FVC) in IPF patients (P<0.001) compared to placebo. The most frequent side effect of nintedanib was diarrhea, with a rate of 61.5% and 18.6% in the nintedanib and placebo group respectively, leading to less than 5% of patients discontinuing active treatment (9).

The third highest cited publication was a phase 3 trial of pirfenidone in patients with IPF also published in *The New England Journal of Medicine* in 2014 and written by King *et al.* In that article, the authors demonstrated that oral administration of pirfenidone 2,403 mg/day significantly delayed the decline of FVC% (the percentage of the predicted FVC) (P<0.001), reduced the decline in the 6-minute walk distance (P=0.04), and improved progression-free survival (P<0.001) compared with placebo. Gastrointestinal and skin adverse reactions were more common in the pirfenidone group, but rarely resulted in discontinuation of treatment (10).

IPF was largely considered untreatable prior to 2014. The appearance of nintedanib and pirfenidone was a milestone in the history of treatment of the disease, and the two research articles on these drugs referred to above have been cited repeatedly as classic, highly cited, and high-quality works.

According to our study, Wells, Maher, and Raghu, have contributed the most publications in the field of IPF. Wells is from the Interstitial Lung Disease Unit, Royal Brompton Hospital, and National Heart and Lung Institute, Imperial College of the UK (11,12), and is the most prolific author, with 115 publications. Maher is from the Respiratory Clinical Research Facility, Royal Brompton Hospital, and National Heart and Lung Institute, Imperial College of the UK (13,14), and is the second most prolific author, with 96 papers while Raghu, with 93 papers, is the third most prolific and is from the Center for Interstitial Lung Diseases, University of Washington in USA (15,16). With both Wells and Maher from the Royal Brompton Hospital of UK, this institution would appear to be a major center for research in IPF. However, there was no collaboration in authorship among the top 10 authors before 2015, which shows that researchers are paying more and more attention to the importance of cooperation in the field.

The publications of Raghu were cited 2,853 times from 2011 to 2020, and that author takes the leading position in terms of both the number of articles and the degree of cooperation with other authors. As a leading authority in the field, Raghu has been the corresponding author in international IPF guidelines several times, including the *Official ATS/ERS/JRS/ALAT Clinical Practice Guidelines of Idiopathic Pulmonary Fibrosis* in 2011, 2015, and 2018, which were published in the *American Journal of Respiratory and Critical Care Medicine*.

We identified three keyword clusters to analyze research hotspots in IPF. In cluster 1 (clinical research), in addition to "patient" and "IPF", the relative high-frequency keywords were "study", "treatment", "therapy", and "survival", suggesting the hotspots of clinical research on IPF are related to treatment and the improvement of survival rates. In clinical drug therapy, the keywords that appear most frequently were "pirfenidone" and "nintedanib". Many studies have shown that these drugs can significantly delay the decline rate of FVC, which may alleviate disease progression and reduce mortality (9,10). In terms of non-pharmacological treatment, the high-frequency keyword was "lung transplantation". While lung transplantation has been shown to improve the quality of life of patients with IPF and improve the survival rate (17), with a 5-year survival rate of 53% (18), its timing and the effect of single or double lung transplantation on the prognosis of patients with IPF requires further study.

In cluster 2 (pathogenesis research), the keywords that appear more frequently were "cell", "disease", "expression", "fibrosis", "pulmonary fibrosis", "TGF beta", "pathway", and "fibroblast". At present, it is generally believed that the pathogenesis of IPF results from the interaction of multiple genetic and environmental risk factors, and among them, repeated local micro-injuries to aging alveolar epithelial cells plays a central role (19). Injured alveolar epithelial cells secrete numerous fibrogenic growth factors, including transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) (19). TGF-β is a strong profibrotic mediator which promotes epithelial mesenchymal transition (EMT), and activates fibroblast proliferation and transformation into myofibroblasts (20). One of the key pathways in IPF is the Wnt/β-catenin pathway, which is activated by TGF-β, and is involved in EMT and fibrogenesis (21). Micro-injuries trigger abnormal epithelial-fibroblast communication, then recruit and activate myofibroblasts. Activated myofibroblasts produce matrix, resulting in a large amount of extracellular matrix accumulation and pulmonary interstitial remodeling (2).

In cluster 3 (diagnosis research), the primary keywords were "level", "control", and "biomarker". Biomarkers can

be used for diagnosis, prognosis, and therapy response monitoring of IPF. Although many potential biomarkers have been studied, including gene expression profiles, CCL18, MMP7, and SPD, none have been verified by prospective clinical practice, and the focus of research in this domain is to verify biomarkers through multicenter collaborative prospective cohort studies (2).

Keywords burst detection was conducted to trace research hotspots and research trends (22). According to the top 25 keywords with the strongest citation bursts, early research placed emphasis on "alveolar epithelial cell", "transforming growth factor β", "myofibroblast", "collagen", "oxidative stress", and "endoplasmic reticulum stress", while recent research has focused on "nintedanib", "safety", "efficacy", "quality of life", and "trial". This indicates research hotspots in IPF seem to have transferred from pathogenesis to treatment, and from foundation medicine to clinical medicine.

There are many studies on the pathogenesis of IPF, and a favored pathogenesis speculates that recurrent subclinical epithelial injury on accelerated epithelial cell aging leads to the aberrant repair of injured alveoli and deposition of collagen fiber by myofibroblasts. Shortened telomeres, oxidative injury, and endoplasmic reticulum stress lead to inhibition of the proliferation of alveolar epithelial cells and stimulation of profibrotic mediator secretion (23). Nonetheless, a comprehensive understanding of IPF pathogenesis remains difficult to realize.

In recent years, the research hotspots of IPF have gradually shifted to its treatment, and significant advances have been made in pharmacotherapy. Two drugs, nintedanib and pirfenidone, are proven to be safe and effective by slowing the rate of FVC decline and potentially improving the quality of life of patients. Nintedanib is a tyrosine kinase inhibitor that targets growth factor pathways, including those downstream of fibroblast growth factor receptor, vascular endothelial growth factor receptor, and PDGF receptor (24). The most common adverse reaction of nintedanib is diarrhea. Pirfenidone has several antifibrotic effects, including the down-regulation of TGF-β, inhibition of collagen synthesis, and reduction in fibroblast proliferation (25). Common side effects of pirfenidone are anorexia, nausea, and photosensitivity. However, which of these medications provides the greatest benefit in individual patients is still unclear.

The accumulation of basic biological knowledge on fiber proliferation has promoted several new drug trials. Researchers have studied the safety, tolerability and pharmacokinetic in patients with nintedanib and pirfenidone combination therapy versus those treated with nintedanib alone, which suggested that nintedanib and pirfenidone combination therapy had manageable levels of safety and tolerability (ClinicalTrials.gov Identifier: NCT02579603). Pamrevlumab is an antibody targeting connective- tissue growth factor, which has shown promise in delaying the decline of FVC compared with placebo. At present, a phase 3, randomized, placebo-controlled, multi-center trial to evaluate its efficacy and safety is ongoing (ClinicalTrials.gov Identifier: NCT03955146).

Previously, IPF was considered in a completely untreatable. Progress has been made in the research and development of pulmonary anti-fibrosis drugs, and the emergence of nintedanib and pirfenidone has provided a milestone breakthrough in the history of IPF treatment. Whereas pirfenidone and nintedanib are currently recommended for patients with mild to moderate pulmonary dysfunction with IPF, their benefit in severe disease is unclear, and adverse reactions may limit their use in some patients. Moreover, the cost of each drug is estimated to more than $100,000 annually (24), which may further limit their application for many patients. Above all, these drugs can only delay the decline rate of FVC, and are unable to reverse its progression, and the survival rate of patients remains very low. Lung transplantation can prolong survival, but the high technical requirements, uncertain survival rate after transplantation, donor lung scarcity, high cost, and other factors objectively limit its implementation in clinical practice.

According to the results of literature analysis, we could conclude that the future research direction will focus on conducting multi-center randomized controlled trials to explore and evaluate the new therapeutic drugs for IPF. Many trials are needed to screen drugs that may halt collagen deposition, have less adverse reactions, and are affordable. A future treatment strategy for IPF may be a combination of multiple drugs targeting different aspects of pulmonary fibrosis, perhaps reducing the need for lung transplantation.

Conclusions

This study utilized information visualization software to evaluate the contributions of countries, institutions, journals and authors, to analyze research hotspots on IPF research over the past decade. The USA took the leading position in this field by contributing the most publications, and the

top five research institutions with the largest number of publications were also from that country. The *American Journal of Respiratory and Critical Care Medicine* attracted the most citations, and had an incontrovertible academic impact, with five of the top 10 high-cited references published in this journal. Raghu was the academic authority in this domain in terms of both the number of publications and the most cited publications. The results also showed that the current research hotspot in the field of IPF is drug therapy largely involving the medications nintedanib and pirfenidone. Future research directions focusing on multi-center randomized controlled trials to explore and evaluate new therapeutic drugs for IPF will rely on the close cooperation of multiple institutions and scholars. Our research identified the authoritative institutions and scholars, indicated the high-cited literatures, and analyzed hotspots and future directions in IPF research. These findings will enable researchers to identify leading institutions and scholars, to seek academic collaboration with leaders in the field, and to keep abreast of current and future directions in IPF research.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-1836). All authors report funding from the China Postdoctoral Science Foundation (grant No. 2019M661163) and the Department of Science and Technology of Liaoning Province, China (grant No. 2019-BS-280). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 The 217 keywords with at least 218 occurrences

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
1	Absence	1	213	261	2016.2	24.11
2	Accumulation	2	212	528	2016.3	31.92
3	Activation	2	215	1,535	2016.5	28.82
4	Activity	2	216	1,328	2016.2	22.33
5	Acute exacerbation	1	212	937	2016.4	37.65
6	Addition	2	216	673	2016.3	26.05
7	AE IPF	1	185	282	2017.4	14.49
8	Age	1	216	1,396	2016.6	25.71
9	Alpha	2	214	871	2016.0	21.81
10	Alpha SMA	2	193	323	2016.5	21.21
11	Alveolar epithelial cell	2	207	415	2016.1	25.71
12	Analysis	1	216	3,154	2016.8	23.72
13	Apoptosis	2	204	738	2016.0	27.63
14	Area	1	216	682	2016.3	19.90
15	Article	1	210	322	2016.0	20.94
16	Association	1	215	839	2016.5	30.80
17	Asthma	2	204	344	2016.5	20.68
18	Autophagy	2	176	266	2016.6	41.40
19	Bal	3	210	261	2015.8	37.34
20	Balf	3	204	340	2016.0	14.97
21	Baseline	1	207	523	2016.9	33.07
22	Beta	2	214	814	2016.2	21.95
23	Biomarker	3	216	998	2016.8	20.90
24	Bleomycin	2	210	1,380	2016.1	22.89
25	BLM	2	197	709	2017.2	14.69
26	Bronchoalveolar lavage fluid	3	211	240	2015.8	19.25
27	Cancer	2	212	451	2016.5	30.91
28	Capacity	1	216	848	2016.3	29.60
29	Carbon monoxide	1	208	326	2016.6	27.99
30	Case	1	215	1,394	2016.0	23.01
31	Cause	1	214	683	2016.3	35.55
32	Cell	2	216	4,908	2016.2	27.24
33	Change	1	216	1,805	2016.5	34.25
34	Chronic	2	215	286	2016.9	20.20
35	Chronic lung disease	2	207	264	2016.7	23.91

Table S1 *(continued)*

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Table S1 *(continued)*

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
36	Chronic obstructive pulmonary disease	2	213	444	2016.5	22.31
37	Clinical trial	1	214	562	2016.4	30.35
38	Cohort	1	209	870	2017.0	32.34
39	Collagen	2	213	717	2016.1	24.33
40	Combination	1	216	317	2016.7	32.66
41	Comorbidity	1	189	349	2017.5	24.54
42	Comparison	1	215	306	2016.7	19.75
43	Concentration	3	216	707	2016.1	17.60
44	Condition	2	216	787	2016.3	20.55
45	Confidence interval	1	197	231	2016.6	27.56
46	Connective tissue disease	1	202	397	2016.4	24.26
47	Contrast	2	216	272	2015.8	26.39
48	Control	3	216	1,155	2015.9	24.85
49	Control group	3	210	267	2016.4	13.15
50	COPD	2	214	589	2016.7	24.84
51	Correlation	1	215	498	2016.1	22.23
52	Cough	1	193	385	2016.5	21.24
53	CTD	1	187	366	2015.9	26.77
54	CTD ILD	1	178	238	2017.1	18.65
55	Cytokine	2	214	483	2016.1	26.57
56	Data	1	216	2,032	2016.6	27.94
57	Day	2	216	1,348	2016.2	27.40
58	Death	1	215	1,007	2016.6	44.67
59	Decline	1	215	819	2017.1	46.98
60	Development	2	216	1,732	2016.5	27.13
61	Diagnosis	1	215	2,648	2016.6	33.36
62	Difference	1	216	806	2016.6	36.10
63	Differentiation	2	213	638	2016.3	32.00
64	Disease	2	216	4,539	2016.5	26.16
65	Disease progression	1	216	623	2016.8	39.32
66	Disease severity	1	211	270	2016.4	24.42
67	DLCO	1	198	490	2016.8	20.62
68	Drug	1	216	882	2017.1	20.14
69	Dyspnea	1	207	350	2016.0	26.52

Table S1 *(continued)*

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Table S1 *(continued)*

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
70	ECM	2	198	351	2017.1	37.46
71	Effect	2	216	2,991	2016.7	22.62
72	Efficacy	1	213	704	2017.0	29.81
73	Emphysema	1	209	568	2016.1	21.12
74	EMT	2	192	663	2016.2	25.57
75	Epithelial mesenchymal transition	2	186	282	2016.2	27.61
76	Evaluation	1	215	614	2016.5	21.21
77	Evidence	1	216	1,120	2016.5	45.07
78	Exposure	2	216	692	2016.3	25.08
79	Expression	2	216	4,204	2016.0	24.72
80	Extent	1	214	456	2015.9	23.42
81	Extracellular matrix	2	211	435	2016.7	37.35
82	Factor	2	216	1,456	2016.5	23.02
83	Fibroblast	2	207	1,865	2016.2	27.83
84	Fibrosis	2	216	3,775	2016.2	31.79
85	Fibrotic disease	2	210	309	2016.5	39.14
86	Function	2	215	1,033	2016.6	26.05
87	FVC	1	213	1,198	2017.0	46.71
88	Gene	2	215	1,306	2016.3	25.97
89	Group	1	216	3,274	2016.7	29.31
90	Growth factor	2	212	635	2015.9	25.12
91	Growth factor beta	2	211	476	2016.0	26.07
92	Hazard ratio	1	196	271	2016.9	43.32
93	Healthy control	3	214	331	2016.7	16.39
94	High resolution	1	202	437	2016.3	26.92
95	HRCT	1	194	580	2016.4	18.46
96	Identification	1	215	302	2016.4	27.98
97	Idiopathic interstitial pneumonia	1	215	493	2015.8	23.36
98	Idiopathic pulmonary fibrosis	1	216	6,718	2016.5	33.77
99	IIP	1	191	576	2016.0	23.07
100	ILD	1	216	3,771	2017.1	18.89
101	Impact	1	216	597	2017.0	21.25
102	Important role	2	213	284	2016.0	21.40
103	Incidence	1	213	566	2016.3	39.04
104	Increase	2	216	760	2016.2	26.86

Table S1 *(continued)*

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Table S1 *(continued)*

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
105	Individual	1	213	360	2015.9	40.72
106	Infection	1	213	620	2016.5	24.61
107	Inflammation	2	216	1,179	2016.3	22.48
108	Inhibition	2	206	700	2016.6	26.28
109	Inhibitor	2	215	929	2016.6	25.56
110	Injury	2	214	806	2016.1	32.78
111	Interstitial lung disease	1	216	2,570	2016.8	20.16
112	Interstitial pneumonia	1	214	899	2015.8	24.88
113	IPF	1	216	10,737	2016.6	25.29
114	IPF lung	2	203	262	2016.1	30.32
115	IPF patient	1	216	1,586	2016.6	17.85
116	January	1	192	217	2016.7	15.86
117	Level	3	216	3,224	2016.3	17.78
118	Life	1	216	625	2016.9	27.66
119	Loss	2	216	489	2016.6	28.99
120	Lung	2	216	2,966	2016.2	26.78
121	Lung cancer	1	215	1,029	2016.6	17.93
122	Lung disease	2	216	1,645	2016.3	27.44
123	Lung fibroblast	2	206	1,109	2016.5	22.78
124	Lung fibrosis	2	216	1,593	2016.4	29.11
125	Lung function	1	216	588	2017.0	29.12
126	Lung injury	2	215	617	2016.0	25.14
127	Lung tissue	2	216	850	2016.5	24.43
128	Lung transplantation	1	209	800	2016.0	18.15
129	Macrophage	2	210	714	2016.8	31.03
130	Management	1	209	818	2016.7	30.60
131	Marker	2	216	898	2016.2	25.22
132	Measurement	1	215	451	2016.4	39.40
133	Mechanism	2	216	1,764	2016.4	31.65
134	Microrna	2	195	265	2016.4	34.46
135	Mir	2	185	1,000	2016.8	29.39
136	Mirna	2	182	282	2016.8	23.54
137	MMP	2	203	487	2015.2	35.06
138	Model	2	216	2,520	2016.6	26.06
139	Month	1	212	1,153	2016.5	24.28

Table S1 *(continued)*

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Table S1 *(continued)*

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
140	Mortality	1	215	1,917	2016.9	26.91
141	Mouse	2	212	2,230	2016.2	24.97
142	Myofibroblast	2	197	647	2015.9	41.16
143	Myofibroblast differentiation	2	185	379	2015.9	38.84
144	Need	1	212	434	2016.7	23.25
145	Nintedanib	1	211	678	2017.8	42.89
146	NSIP	1	200	489	2015.7	15.93
147	Number	1	216	811	2016.2	29.93
148	Outcome	1	216	1,510	2016.8	22.31
149	Oxidative stress	2	204	295	2016.5	24.66
150	Part	2	216	281	2015.8	30.04
151	Participant	1	197	323	2016.9	31.46
152	Pathogenesis	2	216	1,400	2016.2	29.50
153	Pathway	2	215	1,869	2016.7	25.88
154	Patient	1	216	15,676	2016.6	24.20
155	Pattern	1	215	1,497	2016.4	26.81
156	PFD	2	155	259	2017.3	12.59
157	Pirfenidone	1	212	1,284	2016.7	35.35
158	Placebo	1	189	381	2017.0	103.75
159	Poor prognosis	1	215	317	2016.9	18.38
160	Population	1	215	781	2016.4	32.71
161	Presence	1	216	651	2016.0	23.34
162	Present study	2	215	317	2016.5	14.22
163	Prevalence	1	205	489	2016.4	28.19
164	Process	2	216	1,138	2016.2	33.37
165	Production	2	212	707	2016.2	27.23
166	Prognosis	1	215	870	2016.5	24.85
167	Progression	2	216	1,060	2016.8	26.79
168	Proliferation	2	212	1,018	2016.3	27.65
169	Protein	2	216	1,643	2016.1	23.15
170	Pulmonary fibrosis	2	216	3,136	2016.5	23.90
171	Pulmonary function	1	213	246	2016.3	26.28
172	Pulmonary hypertension	1	213	478	2015.8	21.60
173	Quality	1	206	622	2016.9	32.90
174	Range	1	215	449	2016.2	23.59

Table S1 *(continued)*

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Table S1 *(continued)*

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
175	Rat	2	191	480	2016.6	12.44
176	Rate	1	216	1,342	2016.7	30.60
177	Rationale	1	213	244	2016.5	50.89
178	Receptor	2	213	918	2016.2	23.84
179	Regulation	2	206	605	2016.0	29.37
180	Relationship	1	215	475	2016.2	22.76
181	Response	2	216	1,583	2016.3	30.35
182	Review	1	214	1,388	2016.7	26.55
183	Risk	1	215	1,182	2016.6	25.65
184	Risk factor	1	215	572	2017.0	30.19
185	Role	2	216	2,655	2016.4	25.42
186	Safety	1	205	452	2017.0	37.51
187	Sarcoidosis	3	204	445	2016.1	16.31
188	Serum	3	214	402	2015.8	18.80
189	Severity	1	214	455	2016.4	19.13
190	Significant difference	1	214	329	2016.5	24.03
191	SSC	1	208	498	2016.3	25.88
192	Study	1	216	5,961	2016.7	23.55
193	Subject	1	215	1,193	2016.1	30.95
194	Surgical lung biopsy	1	195	278	2015.8	40.13
195	Survival	1	216	2,060	2016.5	29.67
196	Symptom	1	212	575	2016.5	20.32
197	Systemic sclerosis	1	211	378	2016.4	30.69
198	TGF	2	208	463	2016.2	21.61
199	TGF beta	2	215	2,116	2016.2	24.11
200	Therapy	1	216	2,244	2016.7	22.80
201	Time	1	216	1,291	2016.5	31.36
202	Tissue	2	215	803	2016.3	35.06
203	Tomography	1	209	704	2016.4	18.02
204	Total	1	210	402	2017.2	24.39
205	Treatment	1	216	4,142	2016.7	24.39
206	Trial	1	208	851	2016.8	49.65
207	Type	2	216	1,162	2016.1	27.67
208	UIP	1	208	988	2015.9	24.93
209	Understanding	2	216	480	2016.5	27.11

Table S1 *(continued)*

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Table S1 *(continued)*

Rank	Keywords	Cluster	Links	Occurrences	Average publication years	Average citations
210	Use	1	216	913	2016.9	21.54
211	Usual interstitial pneumonia	1	212	479	2015.9	26.39
212	Value	1	216	806	2016.7	22.09
213	Vital capacity	1	213	606	2016.7	37.86
214	Vitro	2	208	539	2016.4	26.26
215	Vivo	2	189	272	2016.6	24.90
216	Week	1	215	649	2016.9	51.69
217	Year	1	216	2,077	2016.6	26.34

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