Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Araiqat B, Syaj S, Al-Khatib A, et al. **A bibliometric analysis of cystic fibrosis transmembrane conductance regulators.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.3004

A bibliometric analysis of cystic fibrosis transmembrane conductance regulators

Bashar Araiqat,[1] Sebawe Syaj,[1] Aseel Al-Khatib,[1] Nour Al-Bzour,[1]
Narmine Hussein,[1] Sarah Aqel,[2] Jamil Ahmad [3]

[1]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan; [2]Medical Research Center, Hamad Medical Corporation, Doha, Qatar; [3]Department of Urology, Hamad Medical Corporation, Doha, Qatar

Correspondence: Bashar Araiqat, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan.
Tel.: +962799086534.
Fax: +962799086534.
E-mail: bbaraiqat189@med.just.edu.jo

Contributions: BA, SS, conceptualization, formal analysis, visualization, writing - original draft; AAK, NAB, NH, data curation, methodology, writing - original draft; SA, JA, supervision, software, data curation, writing - review and editing. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that there is no conflict of interest.

Ethics approval and consent to participate: institutional review board approval was not required for this study as it is a scoping review of publicly available data.

Patient consent for publication: not applicable.

Funding: none.

Availability of data and materials: the data used to support the findings of this study are available from the corresponding author upon request.

Abstract

Cystic fibrosis (CF), a multisystem disease primarily affecting the lungs, arises due to pathogenic mutations in the CF transmembrane conductance regulator (CFTR) gene. This study embarked on a bibliometric analysis to survey the use of CFTR modulators in CF treatment.

Utilizing the Scopus database, a comprehensive search was executed, incorporating terms related to CF and CFTR modulators. Various document types up to July 19, 2023, were included, with citation counts forming the basis of our analyses. Trends, contributor countries, leading institutions, top authors, journals, keywords, and annual citation trends were evaluated.

Our search retrieved 2317 records, predominantly articles. The United States dominated in both publications and citations, followed by the United Kingdom. The University of Alabama, Birmingham, and Vertex Pharmaceuticals, Boston, were among the top institutions. Rowe S.M. was identified as a top-cited author. The Journal of Cystic Fibrosis emerged as the leading journal in terms of publication volume, while the New England Journal of Medicine had the highest citation count. The most-cited article addressed a CFTR potentiator's efficacy in patients with the G551D mutation. The keyword "Cystic fibrosis" appeared most frequently.

This bibliometric analysis underscores the significant research focus on CF, especially concerning CFTR modulators. The results highlight the pivotal role of certain countries, institutions, authors, and journals in the progression of CF research, offering insights into current trends and future research directions.

Key words: cystic fibrosis, CFTR protein, CFTR modulators, bibliometric analysis, Scopus.

Introduction

Cystic fibrosis (CF) is a multisystem disease that affects the lungs, digestive system, sweat glands, and reproductive tract. The primary mechanism is an abnormality in the transfer of sodium and chloride across secretory epithelia caused by pathogenic mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in viscous, thickened secretions in the pancreas, intestines, biliary tract, and reproductive system [1,2].

Progressive lung disease continues to be the leading cause of morbidity and mortality for the vast majority of patients regardless of the fact that the illness is systemic. Findings of genetic and/or functional abnormalities of the CFTR gene provide the basis for the diagnosis of CF. One in every 3200 White Americans, one in every 10,000 Hispanic Americans, one in every

10,500 Native Americans, one in every 15,00 Black Americans, and one in every 30,000 Asian Americans in the United States are estimated to suffer from CF [3,4]. CF is increasingly recognized worldwide, not only in North America, Europe and Australia (regions most familiar with CF) but also in South and East Asia, Africa, and Latin America, although the known prevalence in these regions is lower [5-8].

The diagnosis of CF is established based on consistent clinical symptoms and biochemical or genetic confirmation [9-11]. The primary method of laboratory confirmation is the sweat chloride test, however in some circumstances tests for particular mutations, nasal potential differences (NPD), immunoreactive trypsinogens (IRT), stool fecal fat, or pancreatic enzyme secretion are additionally important.

A class of medications known as CFTR modulators works by enhancing the production, intracellular processing, and/or activity of the CFTR protein, which is inadequate in individuals who have cystic fibrosis. Because they concentrate on the generation or function of the mutant CFTR protein rather than its aftereffects, these medications offer an exceptional advancement in the treatment of cystic fibrosis (CF) [12]. Elexacaftor-tezacaftor-ivacaftor (ETI), a triple combination, is the most used approved modulator. Ivacaftor monotherapy and the dual regimens of tezacaftor and ivacaftor, as well as lumacaftor and ivacaftor, are further approved modulators. The CFTR gene mutations in a particular patient determine their indications and efficacy. Ivacaftor, an oral medication with a small molecular weight, was created especially to treat individuals who have the G551D mutation in at least one CFTR gene. The G551D mutation, which affects 4.4 percent of CF patients, is referred to as a "gating mutation" because it interferes with the regulated opening of the ion channel that the CFTR protein creates [13,14].

In this study, we used a bibliometric analysis to survey the literature related to the use of CFTR modulators in the treatment of CF.

Materials and Methods

Data collection and retrieval methods

We queried the Scopus database using the term “cystic fibrosis” and mutation-related terms like “CFTR”, “phe508del”, and “deltaphe508-cftr”, in addition to terms related to CFTR modulators such as “CFTR/Pharmacology”, “CFTR/Therapeutic use”, “tezacaftor”, “ivacaftor”, and “elexacaftor”. The titles and abstracts were searched for these terms. The search algorithm was as follows:

TITLE-ABS-KEY (cystic AND fibrosis OR ("Cystic Fibrosis/drug therapy" AND cftr OR phe508del OR deltaphe508-cftr OR ("Cystic Fibrosis Transmembrane Conductance Regulator/antagonists and inhibitors" OR "Cystic Fibrosis Transmembrane Conductance

Regulator/drug effects" OR "Cystic Fibrosis Transmembrane Conductance Regulator/genetics" OR "Cystic Fibrosis Transmembrane Conductance Regulator/pharmacology" OR "Cystic Fibrosis Transmembrane Conductance Regulator/therapeutic use")) AND (tezacaftor OR ivacaftor OR elexacaftor))

Articles with missing information or retracted articles were excluded if present. All document types were included: articles, reviews, conference papers, letters, notes, editorials, short surveys, book chapters, and errata. Non-English written articles were also included. The search query was done up to the 19th of July 2023.

Data analysis

Primarily, citation count was the base of our analyses. We analyzed annual trends, countries, institutions, authors, journals, articles, and keywords. Tables and figures were generated using Microsoft Excel from Office 365 (Microsoft Corp., Redmond, WA, USA), VOSViewer (version 1.6.18), and IBM SPSS Statistics (Version 27). Included and excluded studies were demonstrated by a flow chart.

In the keyword analysis, keyword occurrences were limited to a minimum of 100 occurrences. We also manually removed words that implied the study design such as such as “clinical trial,” “retrospective study,” and “case-control,” and redundant words such as “human,” “male,” “female,” and “adult.” We analyzed annual trends by calculating the number of publications in five-year intervals up to 2023, and the mean (± standard deviation) number of citations for all the documents in each group.

Results

Included studies

All documents were included with a total of 2,317 records. Most documents were articles (N = 1,313), and others were reviews (N = 425), or notes, letters, errata, editorials, conference papers, book chapters or short surveys (N = 517). Sixty-two documents were of unknown type (Figure 1).

Countries

We presented a list of the top-contributing countries in terms of documents published and citations earned (Table 1). The United States leads with 1,039 documents and 32,098 citations. The United Kingdom follows with 357 documents and 13,824 citations. Canada, Australia, and Germany make up the rest of the top five contributing countries. The visualization of country contribution and interconnections is shown in Figure 2.

Institutions

In *Supplementary Table 1*, institutions are ranked according to the number of publications and citations. The University of Alabama at Birmingham leads with 120 publications and 10,993 citations. Other highly contributing institutions include Vertex Pharmaceuticals, Boston, and the University of Washington, Seattle, both in the United States. In terms of citations, Vertex Pharmaceuticals, Boston, leads with 11,300 citations, followed by the University of Alabama at Birmingham.

Authors

The list of the top 15 most cited authors was led by Rowe S.M. affiliated at University of Alabama at Birmingham with 83 documents and 8,351 citations (Table 2). McKone E.F., Ramsey B.W., Konstan M.W., and Elborn J.S. and others follow in terms of the number of citations received. A visualization of the authors' collaboration network is shown in Figure 3. A more thorough list of authors is displayed in *Supplementary Table 2.*

Journals

In Table 3, the journals are ranked by the number of publications and citations. The Journal of Cystic Fibrosis has the highest number of publications at 336 and is the second most cited journal. The New England Journal of Medicine, with fewer publications (27), has the highest number of citations. Figure 4 demonstrates the citation network of the top journals.

Top-cited articles

Supplementary Table 3 presents the top 10 most cited articles, the first of which is "A CFTR potentiator in patients with cystic fibrosis and the G551D mutation" by Ramsey B.W., cited 1,676 times.

Key words

Table 4 highlights the top 20 most frequently occurring keywords in the document set. "Cystic fibrosis" appears most frequently, with 2,179 occurrences, followed by "Ivacaftor" (1,798 occurrences) and "Cystic fibrosis transmembrane conductance regulator" (1,551 occurrences) (Figure 5).

Annual trends

In *Supplementary Table 4*, citation trends over time are presented. The period between 2010 and 2015 had a higher average number of citations per document (mean = 38.0, SD = 112.4)

than the periods of 2016-2020 (mean = 26.1, SD = 59.8) and 2021-2023 (mean = 6.35, SD = 13.0) (*Supplementary Figure 1*).

Discussion

Cystic fibrosis (CF) is an incurable lethal autosomal recessive disease in which most patients survive to adulthood [15]. Many organs are affected by this disease but the most severely affected are the lungs [16]. About more than 1000 new cases being diagnosed every year with CF, it is noteworthy to understand the mechanism by which this disease occurs, the genetics role, and other factors that increase its incidence in order to develop early screening approaches, integrated treatment methods, and improve the patient's quality of life [17].

As this disease has taken the interest of many foundations and funding companies, the prognosis has improved significantly from its first diagnosis. Moreover, advancements in the treatment and management of cystic fibrosis have resulted in a significant rise in patient life expectancy, enabling individuals to lead healthier lives and actively participate in the labor force which in turn improved their quality of life [18]. Our aim in conducting this bibliometric study is to assess the research landscape, identify key contributors, and understand the dissemination of knowledge in the cystic fibrosis field.

A previously published bibliometric study was conducted on a European population with non-communicable respiratory diseases CF was one of them, in which the papers included were the most cited in the Web of Science (WoS) and covering articles and reviews from 2002 up to 12 years [19]. In contrast with our study, our research focuses on cystic fibrosis and utilizes the Scopus database to include a diverse range of document types, resulting in a more extensive and current assessment of the literature. By encompassing articles, reviews, conference papers, editorials, book chapters, and meeting abstracts until July 19, 2023, our study captures the latest and most influential publications in the field of cystic fibrosis. Furthermore, we comprehensively explored the correlations between the citations and different factors such as publication year, author's countries, document types, and journals that shed light on emerging trends and citation patterns within cystic fibrosis research. In addition, our study focused solely on cystic fibrosis for which it provides valuable insights that were previously unavailable, and makes it an exceptional resource for researchers, clinicians, and decision-makers in the cystic fibrosis field.

Another bibliometric study that discussed cystic fibrosis as a COVID-19-associated effect, included studies extracted from WoS up to July 12, 2022, reported that cystic fibrosis had the 6^{th} rank with 110 occurrences suggesting a strong association of COVID-19 and cystic fibrosis as one of its possible adverse events. In addition, their journal-wise analysis reported that The

Journal of Cystic Fibrosis was the top journal in terms of the most published papers on post-COVID-19 fibrosis which further support their correlation [20]. It is critical to understand and take into account these findings for the development of therapeutic approaches and a better understanding of the pathophysiology of the emergence of the disease.

The early screening and diagnosis of cystic fibrosis is a crucial step in improving the prognosis. This has been reported by Bell et al. in a study that was included in our analysis which discussed how the development of diagnostic methods has contributed to improved outcomes of the patients. In addition, it is important to manage the symptoms according to the different disease stages and age groups [21]. These findings were also supported by Cutting et al. in a study that was one of the topmost cited articles. They reported that in addition to the fact that early screening of newborns and population groups allows for proactive management of individuals affected by cystic fibrosis right from birth, analyzing genomic variations will offer insights into the expected trajectories for each patient. Genetics has been and will remain pivotal in ensuring a better and more normal lifespan for those living with cystic fibrosis [22].

For the therapeutic management of cystic fibrosis, many clinical trials have been conducted across different populations. Newly updated guidelines have been published by the American Journal of Respiratory and Critical Care Medicine which was one of the top journals in terms of publications and citations count [23]. Their guidelines were based on systematic reviews of the available literature, and they highlighted the importance of making individualized decisions regarding therapy based on each case scenario and the provided recommendations.

The research on cystic fibrosis, which sometimes is called mucoviscidosis, has increased due to the increase in the charities that support and fund these studies. Undoubtedly, this disease predominantly impacts young people, given the considerably low life expectancy, however, with the availability of improved treatments and the increased research efforts, the life expectancy has increased to approximately 40 years which is a huge improvement [24]. Our analysis reported that the top contributions were from the United States followed by the United Kingdom and Canada. The top 10 cited articles discussed the diseases on the genetic level, the possible treatments and management protocols across different countries, in addition to the future outlook of cystic fibrosis on a global scale.

The strength of our study compared to the previously published studies is that we solely focused on cystic fibrosis and included all the countries without any filtration. However, our study has some limitations. Firstly, our search was limited to the Scopus database, and we did not include searches on the Web of Science Core Collection or Google Scholar. Secondly, we did not conduct separate filtering for open-access versus subscription-based publications,

which might have influenced the frequency of article citations. Hence, we recommend for future studies to include the articles from these resources to establish a robust conclusion.

Conclusions

In conclusion, the main focus of our review was to present a valuable bibliometric perspective on the resources available for cystic fibrosis. Furthermore, we offered an overview of the current areas of active research and made predictions about future frontiers by visually analyzing the literature.

References

1. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. N Engl J Med 2005;352:1992-2001.
2. Ratjen F, Döring G. Cystic fibrosis. Lancet 2003;361:681-9.
3. Hamosh A, FitzSimmons SC, Macek MJ, et al. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr 1998;132:255-9.
4. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet 2009;373:1891-904.
5. Stewart C, Pepper MS. Cystic fibrosis on the African continent. Genet Med 2016;18:653-62.
6. Yamashiro Y, Shimizu T, Oguchi S, et al. The estimated incidence of cystic fibrosis in Japan. J Pediatr Gastroenterol Nutr 1997;24:544-7.
7. Guo X, Liu K, Liu Y, et al. Clinical and genetic characteristics of cystic fibrosis in CHINESE patients: a systemic review of reported cases. Orphanet J Rare Dis 2018;13:224.
8. Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros 2022;21:456-62.
9. Yankaskas JR, Marshall BC, Sufian B, et al. Cystic fibrosis adult care: consensus conference report. Chest 2004;125:1S-39S.
10. Stern RC. The diagnosis of cystic fibrosis. N Engl J Med 1997;336:487-91.
11. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr 1998;132:589-95.
12. Middleton PG, Taylor-Cousar JL. Development of elexacaftor - tezacaftor - ivacaftor: highly effective CFTR modulation for the majority of people with Cystic Fibrosis. Expert Rev Respir Med 2021;15:723-35.
13. Skilton M, Krishan A, Patel S, et al. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. Cochrane Database Syst Rev 2019;1:CD009841.

14. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663-72.
15. De Boeck K. Cystic fibrosis in the year 2020: a disease with a new face. Acta Paediatr 2020;109:893-9.
16. Reis FJC, Damaceno N. Cystic fibrosis. J Pediatr (Rio J) 1998;74:S76-94. [Article in Portuguese].
17. Klimova B, Kuca K, Novotny M, Maresova P. Cystic fibrosis revisited - a review study. Med Chem 2017;13:102-9.
18. Leso V, Romano R, Santocono C, et al. The impact of cystic fibrosis on the working life of patients: a systematic review. J Cyst Fibros 2022;21:361-9.
19. Begum M, Lewison G, Wright JSF, et al. European non-communicable respiratory disease research, 2002-13: bibliometric study of outputs and funding. PLoS One 2016;11:e0154197.
20. Zhong H, Zhou Y, Mei SY, et al. Scars of COVID-19: a bibliometric analysis of post-COVID-19 fibrosis. Front Public Health 2022;10:967829.
21. Bell SC, Mall MA, Gutierrez H, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8:65-124.
22. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet 2015;16:45-56.
23. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2013;187:680-9.
24. Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. Eur Respir J 2007;29:522-6.

Online supplementary material

Supplementary Table 1. Top-contributing institutions according to the number of publications, and citations.

Supplementary Table 2. Top cited authors.

Supplementary Table 3. Top 10 most cited articles.

Supplementary Table 4. Year trends and the number of citations per year.

Supplementary Figure 1. Annual trends mean citation and publication counts.

Table 1. Publications and citations of the top-contributing countries.

Country	Documents	Citations
United States	1,039	32,098
United Kingdom	357	13,824
Canada	208	12,451
Australia	156	8,709
Germany	191	8,609
Republic of Ireland	95	8,493
France	173	7,201
Belgium	75	5,192
Netherlands	101	4,468
Italy	180	3,850
Czech Republic	23	3,459
Israel	46	1,973
Portugal	40	1,161
Switzerland	42	1,135
India	17	738
New Zealand	11	638
Spain	49	631
Russia	23	515
South Africa	8	484
Singapore	3	471
Argentina	1	454
Hungary	11	419
China	32	391
Japan	16	303
Sweden	20	287

Table 2. Top 15 most cited authors.

Author	Documents	Citations
Rowe S.M.	83	8,351
Mckone E.F.	34	6,318
Ramsey B.W.	29	5,691
Konstan M.W.	25	4,351
Elborn J.S.	29	4,170
Tullis E.	15	4,136
Ratjen F.	40	3,931
Waltz D.	18	3,844
Wainwright C.E.	17	3,640
Davies J.C.	47	3,112
Marigowda G.	13	3,099
Taylor-Cousar J.L.	39	2,872
Mall M.A.	36	2,786
Simard C.	9	2,709
Munck A.	12	2,592

Table 3. Number of publications and citations for the most cited journals.

Journal – Publication count sorted	Publications	Citations
Journal of Cystic Fibrosis	336	5,351
Pediatric Pulmonology	109	1,082
American Journal of Respiratory and Critical Care Medicine	94	3,831
The Lancet Respiratory Medicine	54	3,199
European Respiratory Journal	46	933
International Journal of Molecular Sciences	41	316
Frontiers In Pharmacology	38	697
Annals of the American Thoracic Society	34	798
Paediatric Respiratory Reviews	32	257
Chest	28	1,129
New England Journal of Medicine	27	6,159
Thorax	25	526
American Journal of Physiology - Lung Cellular and Molecular Physiology	23	525
Journal of Personalized Medicine	22	149
ERJ Open Research	21	231
Journal – Citation sorted	**Publications**	**Citations**
New England Journal of Medicine	27	6,159
Journal of Cystic Fibrosis	336	5,351
American Journal of Respiratory and Critical Care Medicine	94	3,831
The Lancet Respiratory Medicine	54	3,199
Nature Medicine	10	1,441
Chest	28	1,129
Pediatric Pulmonology	109	1,082
Science Translational Medicine	10	1,006

European Respiratory Journal	46	933
The Lancet	12	847
Annals of the American Thoracic Society	34	798
Frontiers In Pharmacology	38	697
Nature Reviews Genetics	1	584
Thorax	25	526
American Journal of Physiology - Lung Cellular and Molecular Physiology	23	525

Table 4. Top 20 most occurring keywords.

ID	Keywords	Occurrences
1	Cystic fibrosis	2,179
2	Ivacaftor	1,798
3	Cystic fibrosis transmembrane conductance regulator	1,551
4	Genetics	928
5	Aminophenols	829
6	Aminophenol derivative	788
7	Quinolones	723
8	Forced expiratory volume	687
9	Quinolone derivative	686
10	Gene mutation	685
11	Lumacaftor	659
12	Mutation	650
13	Ivacaftor plus lumacaftor	522
14	Tezacaftor	479
15	Lung function	469
16	Benzodioxoles	462
17	1,3 benzodioxole derivative	461
18	CFTR protein	443
19	Drug efficacy	437
20	Metabolism	411

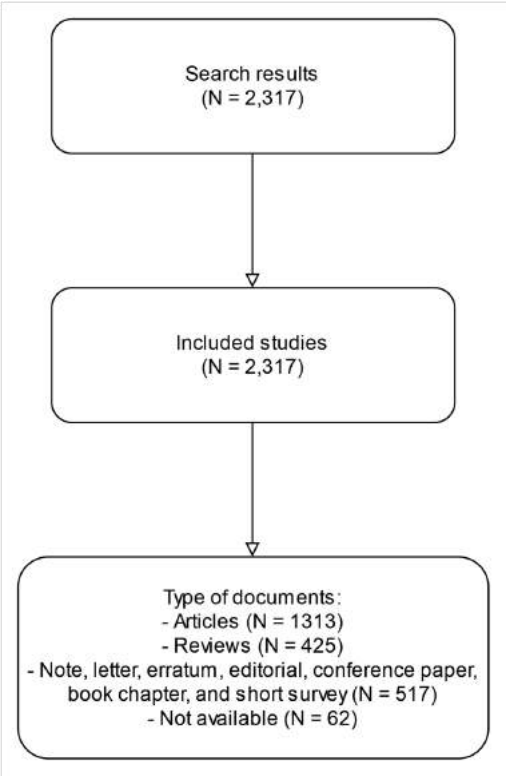

Figure 1. Flow chart of search results and exclusion criteria.

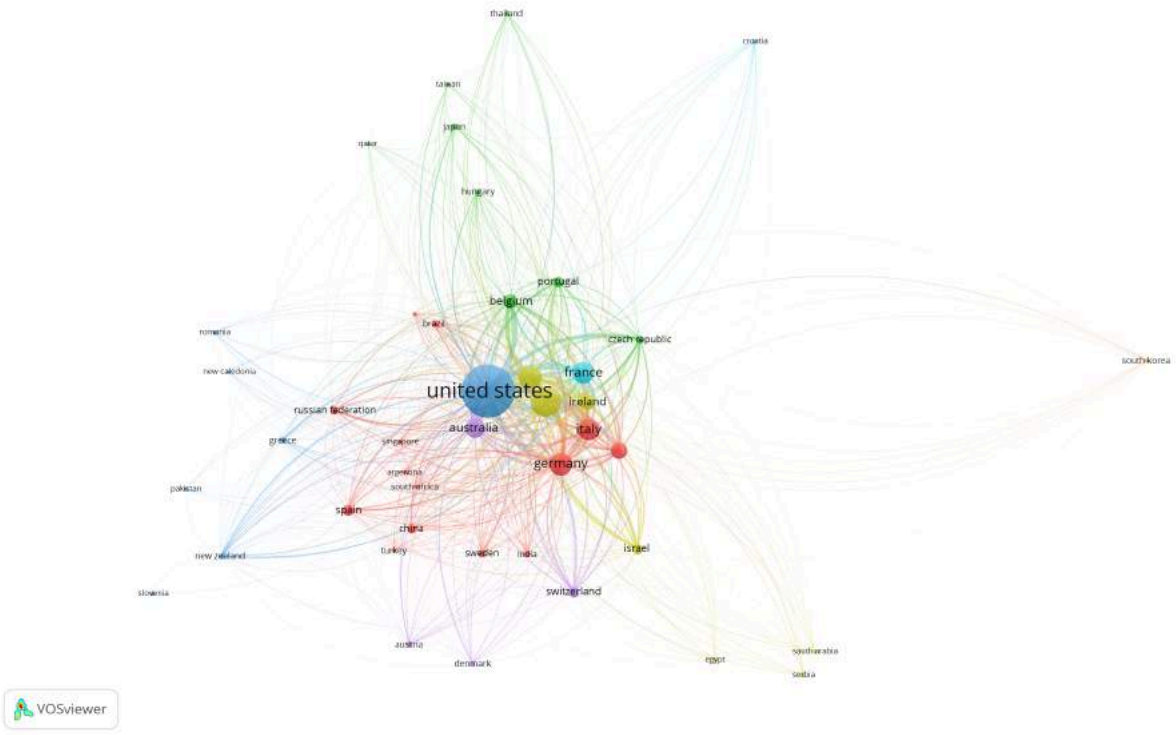

Figure 2. Countries visualization.

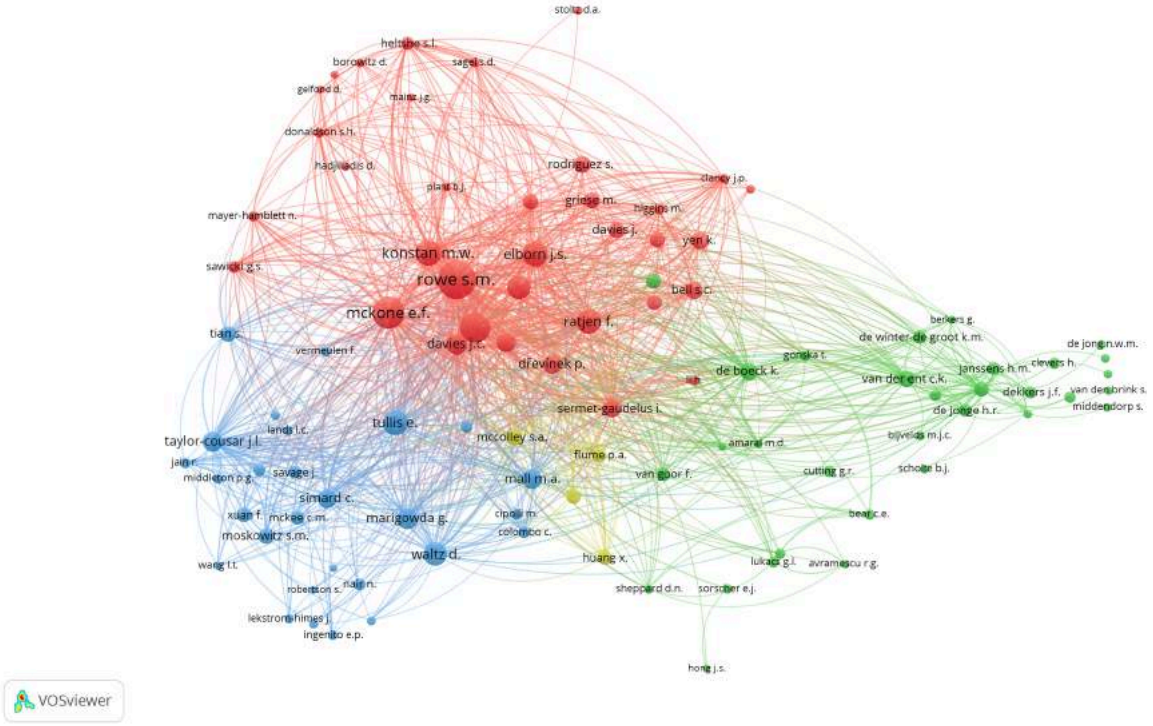

Figure 3. Visualization of the most cited authors.

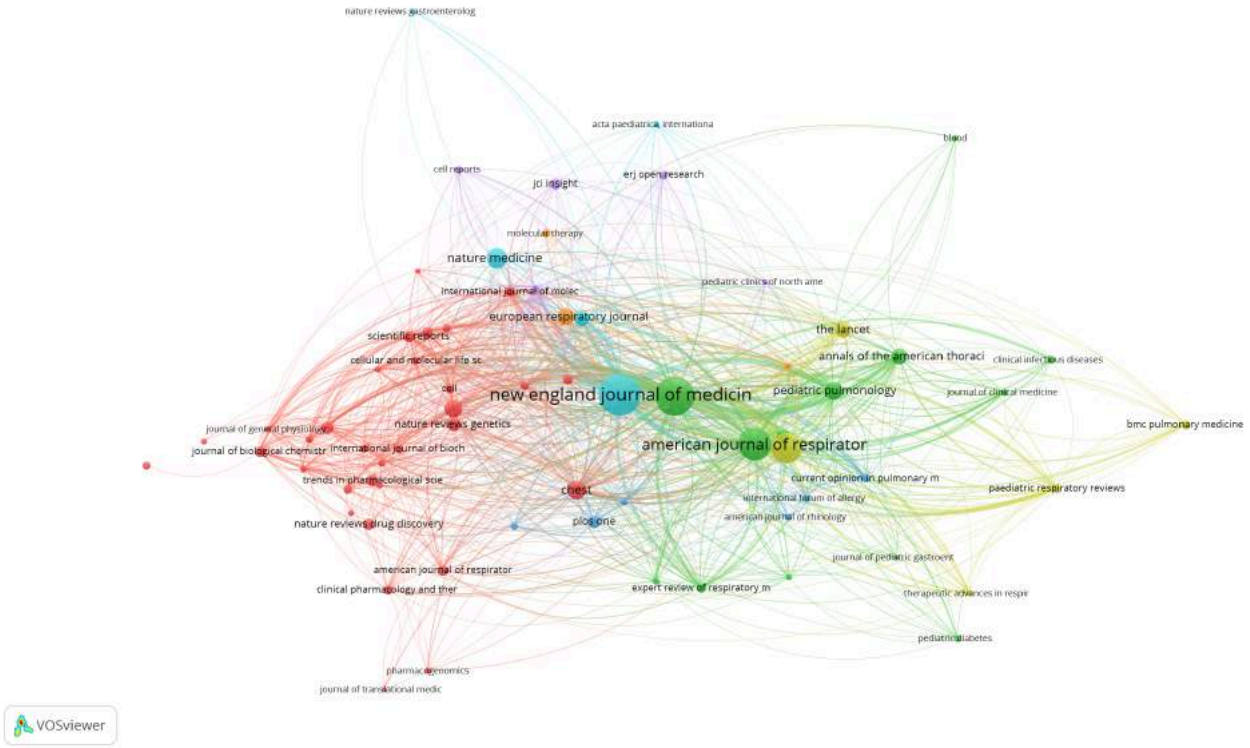

Figure 4. Visualization of the most cited journals.

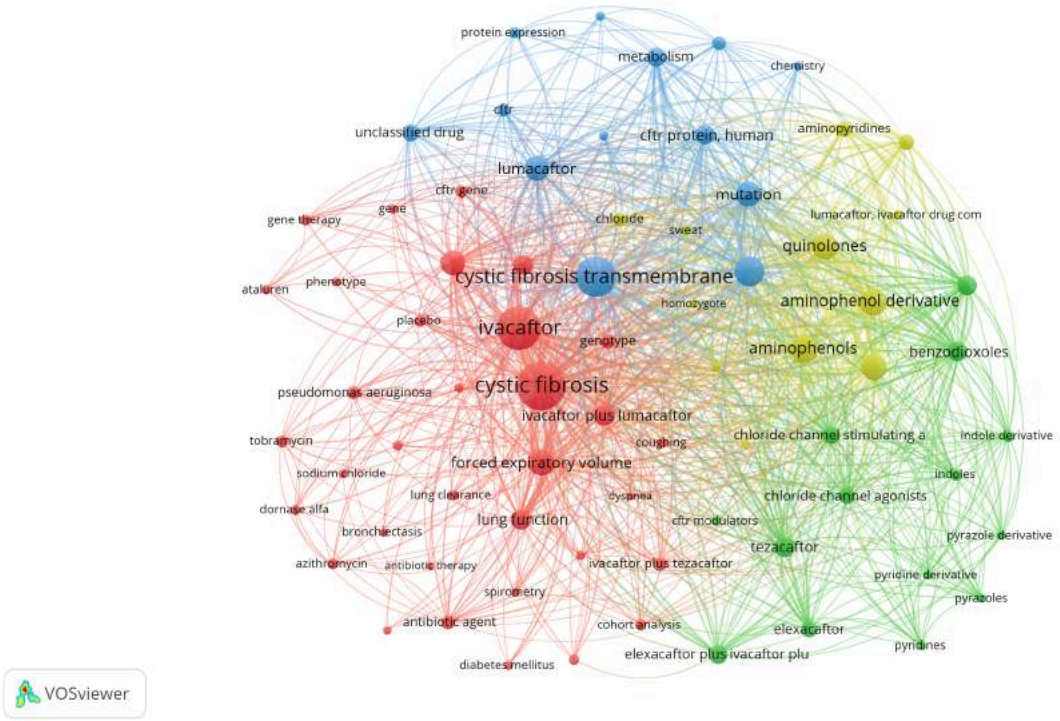

Figure 5. Visualization of the most occurring keywords and their interconnection across the years.