Original Article

Emerging trends and hotspots in animal experimental research on lung transplantation from 2004 to 2023: a bibliometric analysis

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Background: Lung transplantation is the only viable option for end-stage respiratory diseases, with the global prevalence of this procedure on the rise in recent years. However, it is still plagued by various complications, for which no satisfactory therapy has yet been identified. Understanding the mechanisms underlying these post-transplant complications may be beneficial to enhance patient outcomes. This study utilized bibliometric analysis to assess present publication trends and focal points in the field of animal experimental studies on lung transplantation, aiming to provide insights into potential areas for future research.

Methods: Utilizing CiteSpace software, the Online Analysis Platform of Literature Metrology, R package bibliometrix and VOSviewer, an analysis of current publication trends and hotspots in the area of animal experimental research for lung transplantation was carried out for the period spanning from 2004 to 2023. The English articles were searched in the Science Citation Index-Expanded (SCI-E) of Web of Science Core Collection (WoSCC).

Results: A total of 995 articles on animal experimental research on lung transplantation over the past two decades were retrieved. Rats, mice and swine were the most commonly used animal models, with orthotopic lung transplantation, ischemia-reperfusion (IR), and ex vivo lung perfusion (EVLP) being the most frequently employed model of lung transplantation in animals. The leading contributed countries in this area were USA, Canada, Japan and China. Washington University and Shaf Keshavjee were acknowledged as the most influential institute and scholar, respectively. The top 10 main clusters identified through co-occurrence cluster analysis included, *ex-vivo* lung perfusion, EVLP, obliterative bronchiolitis, necroptosis, bronchiolitis obliterans, non-heart-beating donor, donation after circulatory death, xenotransplantation, hydrogen sulfide and alveolar macrophage. Current research focused on lung IR injury, lung transplant, hypoxia, and differentiation, as revealed by keyword burst detection.

Conclusions: Over the past 20 years, global publications on animal experimental research for lung transplantation have grown rapidly. The current research hotspots focus on lung IR injury, hypoxia and differentiation during lung transplantation. Exploring the potential synergistic effects of EVLP and necroptosis inhibition in more depth could offer valuable information for improving lung transplant outcomes. Our analysis presents a detailed overview of the current state of animal experimental research in lung transplantation, evaluating current publication trends and focal points and providing significant insights for future research efforts.

Keywords: Lung transplantation; animal model; bibliometric analysis; CiteSpace; hotspots

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Introduction

Lung transplantation is the only effective treatment for end-stage respiratory diseases globally. Since the Toronto Group's first successful operation in 1983 (1), the number of lung transplantation procedures has been on the rise. More than 70,000 lung transplantations have been performed worldwide up to now and each providing an opportunity for a recipient to regain quality of life and longevity. The most recent analysis of both the Organ Procurement and Transplantation Network Database and International Society for Heart and Lung Transplantation (ISHLT) reveals that the current overall unconditional 5-year survival rate following lung transplantation is 55–60% (2,3). Despite small strides continued to be made to extend median survival time following lung transplantation, the 5-year survival for lung transplantation is trailing behind 5-year kidney and heart and survival at 88.1% and 85%, respectively (4).

Lung transplantation is always accompanied by numerous complications, such as primary graft dysfunction (PGD), surgical complications, rejection, chronic lung allograft dysfunction (CLAD), and so on (5). PGD occurs in approximately 30% of patients undergoing lung transplantation, representing one of the leading causes of early morbidity and mortality, and plays a crucial role in the development of later CLAD (6). Various studies have demonstrated that the complexities of challenges or damages during lung transplantation involve highly intricate mechanisms such as hyperinflammation, innate immune response, and microbiota (7-9). For instance, inflammasome, damage associated molecular patterns (DAMPs), alloimmunization, interleukin (IL), necroptosis, pyroptosis, etc. all play interconnected roles in the pathophysiological process of lung transplantation at differences stages and levels (10-12). Nevertheless, the exact pathophysiologic mechanism remains not entirely clear and no satisfactory therapy has been identified based on the current understanding of the molecular and cellular mechanisms involved in lung transplantation.

A reliable animal model, which accurately recapitulates the process of lung transplantation *in vivo*, is an important instrument for understanding the mechanism of lung transplantation pathogenesis, enhancing the function of the transplanted organ and improving the overall outcome of lung transplantation. Nonetheless, the complexity of the procedure, especially when performed on mice, can make it difficult for new researchers to select a suitable animal model and accurately execute lung transplantation. Despite the completion of increasing basic studies on lung transplantation using rats, mice, swine and other animals (13-15), there are still fewer basic researches on lung transplantation in comparison to clinical studies. Therefore, gaining knowledge of the latest techniques and identifying the research hotspot in the field of animal experimental research on lung transplantation may be beneficial for future studies to forge new paths and delve into more intricate content.

Bibliometric analysis, a quantitative tool, utilizes mathematical and statistical methods to provide a comprehensive overview of a specific research field. By analyzing parameters like publication numbers, authorship, references, keywords, and more from selected publications within a set timeframe, it provides valuable insights (16,17). Although this analysis method has been widely used in many fields, there has been no bibliometric article focusing on basic lung transplantation research. Consequently, our current study delves into historical and current

Highlight box

Key findings

- This study represents the first bibliometric analysis of research relating to animal experimental research on lung transplantation.
- Rats and mice and swine were the most commonly used animal models. The most frequently employed model of lung transplantation in animals involves orthotopic lung transplantation, ischemia-reperfusion (IR), and ex vivo lung perfusion (EVLP).
- The USA topped the list in publication count, total citations and international collaborative.
- Washington University and Shaf Keshavjee were the most productive institution and scholar, respectively.
- Lung IR injury, lung transplant, hypoxia, and differentiation are current research hotspots.

What is known and what is new?

- Global publications on animal experimental research for lung transplantation have grown rapidly during the past two decades. Both EVLP and necroptosis inhibition have been proven to be utilized to improve the condition of the donor lungs.
- This study found that the relationship between EVLP and necroptosis remains unexplored in published research, indicating a need for further investigation.

What is the implication, and what should change now?

- The gap in knowledge between EVLP and necroptosis could open up a new area of basic research in the field of lung transplantation.
- A deeper exploration into the potential synergistic benefits of combining EVLP with necroptosis inhibition for improving outcomes of lung transplantation is recommended.

publication trends in animal experimental research on lung transplantation, and seeks to identify potential research gaps and future directions in this area through an analysis of publications from 2004 to 2023.

Methods

Data sources and search strategies

Extracted from the Web of Science Core Collection (WoSCC), the data for this study spans from January 1st, 2004 to December 31st, 2023. The data extraction and downloads were carried out on July 20, 2024, to avoid any bias in database updates, ensuring that all processes were completed on the same day. The relevant publications were retrieved in WoSCC by using the following search strategy: Topic Search (TS) = ((“lung transplantation” OR “lung transplant” OR “pulmonary transplantation” OR “pulmonary transplant”) AND (“animal model” OR “mouse” OR “mice” OR “rat” OR “murine” OR “pig” OR “swine” OR “dog” OR “canine” OR “rabbit” OR “primate” OR “gorilla” OR “monkey”)) and Document type=Article and Language=English. Exclusion criteria included: (I) document types other than articles (such as meta-analysis, reviews, book chapter, conference summaries comments, letters, editorial material, and others); (II) no statements relating to lung transplantation or basic research, and (III) repeated publishing. The raw data was obtained from WoSCC in the form of text files containing complete records, specifically focusing on the Science Citation Index-Expanded (SCI-E). Upon completion of the primary data search, two researchers (C.X. and X.T.) independently reviewed all manuscripts to confirm their relevance to the focus of this study. *Figure 1* displays a thorough flowchart outlining the criteria utilized for the inclusion and exclusion of publications.

Analysis of bibliometric online platform

All data, complete with all referenced sources and records meeting the requirements from WoSCC (http://wcs.webofknowledge.com) database were downloaded and saved as .txt files. They were then imported into the Online Analysis Platform of Literature Metrology (https://bibliometric.com/app), R package bibliometrix, CiteSpace V6.2.R7 (Drexel University, Philadelphia, USA), and VOS viewer 1.6.19 (Leiden University, Leiden, The Netherlands) for further analysis in order to describe all literature characteristics regarding basic lung transplantation research.

Utilizing the Online Analysis Platform of Literature Metrology, a histogram was produced to show the annual publication trends across various countries. Additionally, the top 10 highly-cited journals in the field of animal experimental research on lung transplantation were pinpointed. The R package bibliometrix was used to generate the keyword cloud, which consisted of the top 100 high-frequency keywords. The partnerships among countries/regions and institutions were examined and visualized using VOSviewer software. Each node represented a specific country/region, with the links indicating the extent of international cooperation between them. When a node is larger, it signifies a higher number of publications, and a wider line indicates a stronger relationship. CiteSpace, the most recognized and popular bibliometric visualization tool, was utilized to generate multiple figures in order to understand the current state of animal experimental research on lung transplantation and uncover potential hotspots in this field. This included co-citation analysis, author collaboration, citation bursts, networks of clustered co-cited references and keywords with the strongest citation bursts. The knowledge maps visualization was created by utilizing different nodes and links of different sizes. Each map contained varying nodes that represented elements such as an author, cited reference, and links between nodes reveal relationships of collaboration or co-citations.

Results

Quantity, animal models and trends analysis of published papers

Out of the SCI-E of WoSCC, a total of 1,877 articles published from 2004 to 2023 met our inclusion criteria. After screening, 882 publications were excluded, with 330 articles being excluded due to improper article types or language, and remaining 552 being unrelated to our topic (*Figure 1*). Finally, our study encompassed 995 articles on animal experimental research in lung transplantation that were published between 2004 and 2023.

Figure 2A displays the number of articles published per year. With only 32 articles each, 2004 and 2010 saw the lowest number of publications, while 2013 and 2019 had the highest number of publications, with 65 articles each. The annual number of publications seems to fluctuate in a sinusoidal pattern, with both increases

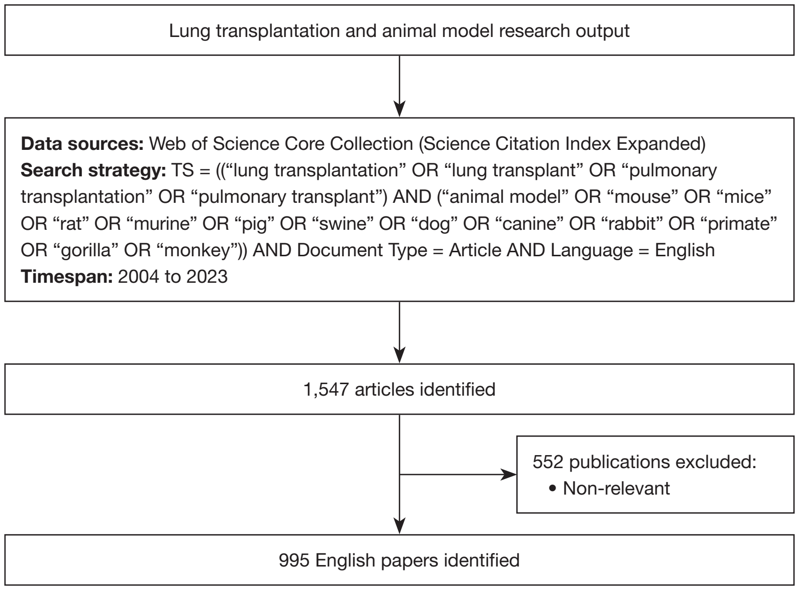


Figure 1 Flowchart for including and excluding publications. TS, Topic Search.

and decreases occurring over time. Using Microsoft Excel 2021, we developed a growth trend mode as follows: $f(x) = -0.0032x^2 + 1.0459x + 39.275$ (R^2=0.3407), which predicted approximately 65 and 74 articles would be published by 2030 and 2040, respectively. In general, the quantity of publications per year is on a slow but steady rise.

The analysis of 995 publications revealed that rats, mice, and swine were the predominant animal models employed, with 364, 363, and 180 studies conducted with these species, respectively. *Figure 2B* illustrates the annual quantity of lung transplantation publications for studies on each of these three animal models. The amount of publications on swine studies has remained relatively stable over time. Despite the nearly equal number of research papers on rat and mouse lung transplantation, the trend over time varies. The annual publications for rat studies have been decreasing slightly, especially in comparison to the recent 10 years. In contrast, the annual number of publications for mouse studies has been steadily increasing over time. Overall, the employment of animal models in basic lung transplantation research has shown a gradual uptick over time, with more researchers opting for mouse models in recent years. The models commonly used for lung transplantation in rats, mice, and swine can be seen in *Figure 2C-2E*. Orthotopic lung transplantation is the preferred method in all rats and mice, with the mouse model experiencing a steady rise in adoption. Additionally, the lung ischemia-reperfusion (IR) model is also commonly utilized in both rats and mice. The model of obliterative bronchiolitis (OB) after lung transplantation, known as heterotopic tracheal transplantation, is predominantly utilized in mice. The main model for studying CLAD, which involves major histocompatibility complex (MHC) I-mismatched lung transplantation, has predominantly been carried out in mice. However, the overall volume of research utilizing these animals for this purpose is relatively small. In addition, swine have been the main subjects of ex vivo lung perfusion (EVLP) models over the past two decades.

The respective contributions of the main countries are shown in *Figure 2F*. Nearly half of the publications are originated in the USA, which contributed 398 articles, followed by Japan and China, which have almost an equal number of publications at around 174 and 172, respectively. The USA consistently leads in the number of publications each year. Japan has seen a steady annual number of articles, whereas China has witnessed a gradual increase in publications since 2015.

The number of citations received by an article in a particular research field is a measure of its impact. In *Figure 2G*, the total number of citations for all publications by each country is displayed, highlighting the top 10 countries based on publication count. In the past 20 years, the USA had the highest number of publication citations (n=11,405), with Japan (n=3,091) and China (n=2,440) coming in second and third. The top 10 countries with the highest mean number of citations for animal experimental

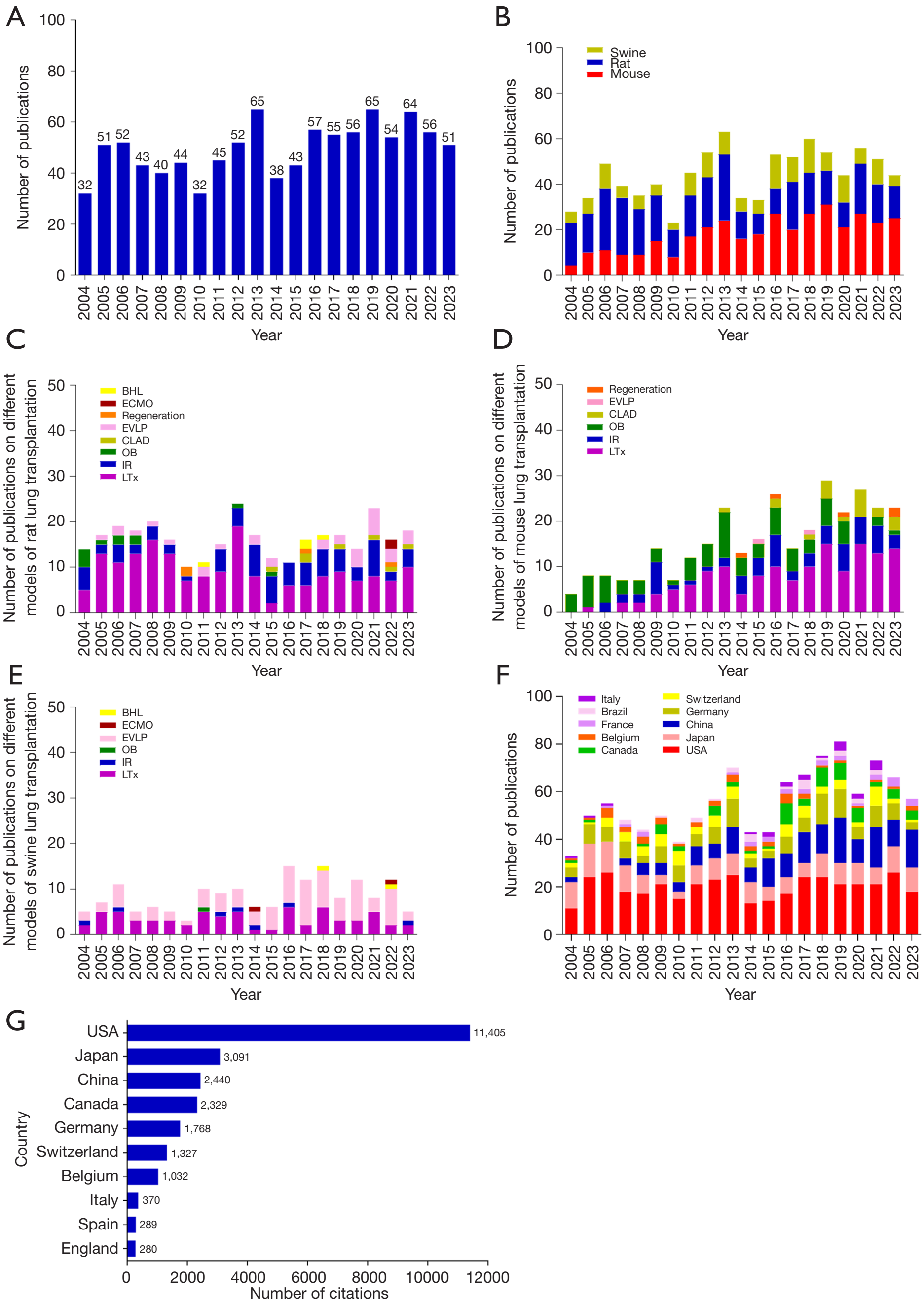


Figure 2 Analysis of the quantity, animal objects and trends of published papers regarding animal experimental research on lung transplantation from 2004 to 2023. (A) The number of annual research publications regarding the experimental lung transplantation research on swine, rat and mouse model from 2004 to 2023. (B) The number of annual research publications regarding the animal experimental study on lung transplantation from 2004 to 2023. (C) The number of annual research publications on different models of rat lung transplantation from 2004 to 2023. (D) The number of annual research publications on different models of mouse lung transplantation from 2004 to 2023. (E) The number of annual research publications on different models of swine lung transplantation from 2004 to 2023. (F) The number of annual research publications and growth trends of the top 10 countries regarding the animal experimental study on lung transplantation from 2004 to 2023. (G) The top 10 countries with the highest total number of citations. BHL, biohybrid lung; ECMO, extracorporeal membrane oxygenation; EVLP, ex vivo lung perfusion; CLAD, chronic lung allograft dysfunction; OB, obliterative bronchiolitis; IR, ischemia-reperfusion; LTx, lung transplantation.

Table 1 The top 10 countries with the highest average number of citations per article from 995 retrieved list for animal experimental studies on lung transplantation from 2004 to 2023 (sorted by the average number of citations)

Rank	Country	Total number of citations	Number of publications	Average number of citations
1	Canada	2,329	63	36.97
2	USA	11,405	400	28.51
3	Denmark	218	8	27.25
4	Belgium	1,032	39	26.46
5	Austria	277	13	21.31
6	Switzerland	1,327	72	18.43
7	Australia	110	6	18.33
8	Sweden	219	12	18.25
9	Japan	3,091	174	17.76
10	Italy	370	21	17.62

research on lung transplantation between 2004 and 2023 are ranked in *Table 1*. Canada, USA and Denmark were ranked first, second and third, respectively, in terms of average publication citations, with numbers of 36.97, 28.51, and 27.25. Japan, despite being second for total publication citations, ranked ninth in average citations per article at 17.76. China, on the other hand, had a lower average publication citation of 14.35, placing it outside of the top 10. Additionally, North Ireland and Russia, each with only one article published, had a mean publication citation number of 41 and 28, respectively. Due to the limited data from the two countries, they were not included in *Table 1* to avoid bias and allow for a more accurate analysis.

Analysis of cooperation between countries and institutions

Over the last 20 years, articles on animal experimental research in lung transplantation have been released by a minimum of 878 institutions across 39 various countries. The distribution map of countries is illustrated in *Figure 3A*. The diagram depicts the scholarly collaboration between countries in field of basic lung transplantation research. The USA was identified as the country that cooperated the most with other countries, followed by Japan, Germany, Switzerland, China, Belgium, Canada, England, Italy, and France. *Figure 3B* illustrates a distribution map of institutions. The top 10 productive institutions were Washington University (n=62), University of Toronto (n=52), Hannover Medical School (n=50), University of Pittsburgh (n=36), University Zurich Hospital (n=33), Okayama University (n=32), University of Virginia (n=29), Kyoto University (n=27), Harvard University (n=26), and Harbin Medical University (n=26), respectively. Moreover, the top 3 institutions engaged in the most collaborations were Washington University, University of Toronto, and University Health Network (UHN), orderly.

Co-authorship network and distribution of core author

During the last two decades, 5,603 authors made substantial contributions to the publication outputs, with the top 10 most productive authors highlighted in *Figure 4*. Shaf Keshavjee from University of Toronto, contributed the most articles (n=38), followed by Mingyao Liu from University of Toronto (n=35), Kron IL from University of Virginia (n=25), Cypel Marcelo from University of Toronto (n=24), Weder Walter from University Zurich Hospita (n=24), Laubach VE from University of Virginia (n=21), Inci Ilhan from University Zurich Hospital (n=21), Jungraithmayr Wolfgang University Zurich Hospital (n=21), Date Hiroshi from Kyoto University (n=20) and Kreisel Daniel from Washington University (n=19).

Journal analysis

Over the past 20 years, 195 journals published the retrieved 995 original articles concerning animal experimental research on lung transplantation. The top 10 most active journals, ranked by the total number of citations received for the articles they have published, are listed in *Table 2*. Out

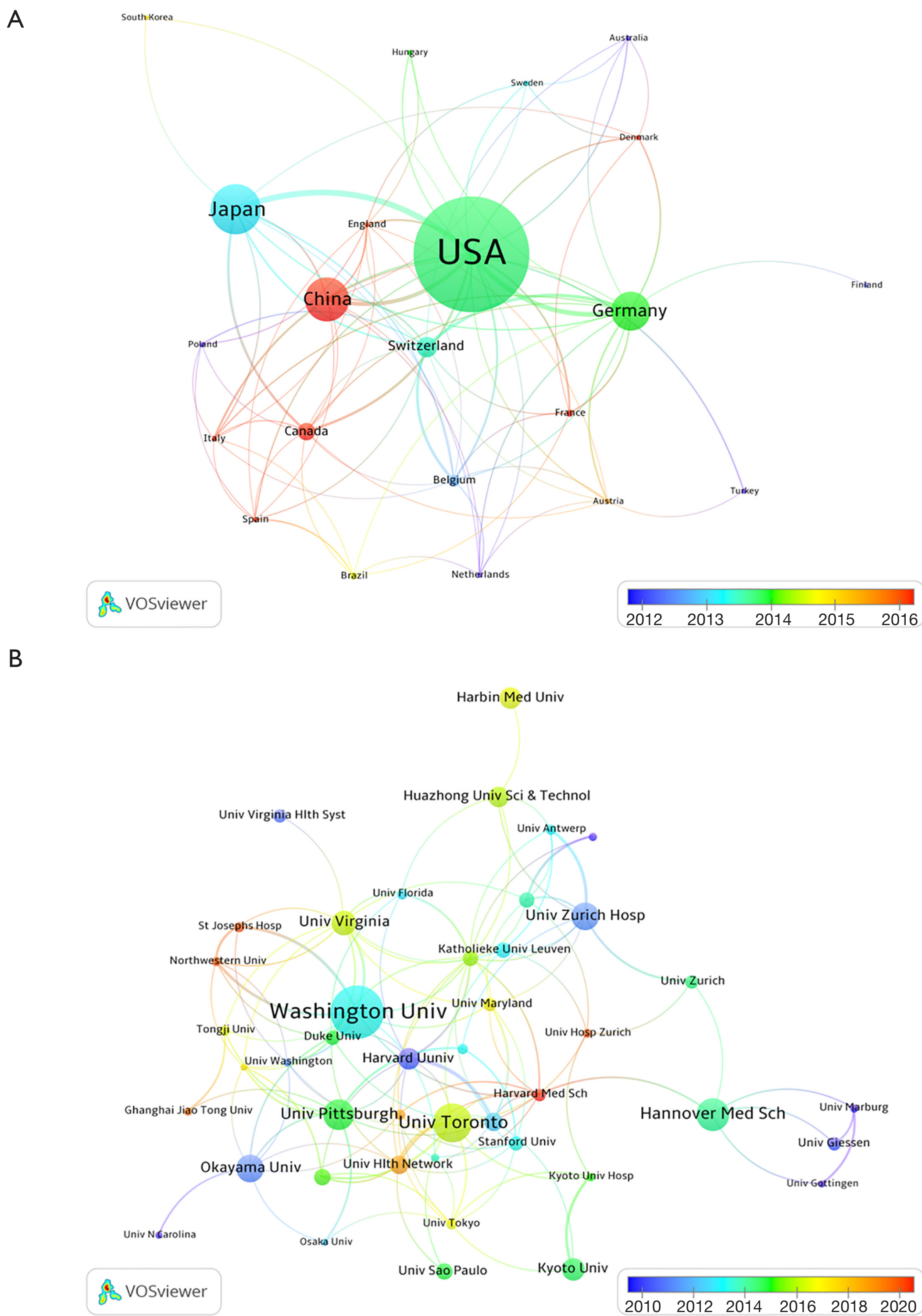


Figure 3 VOSviewer network map of the collaboration analysis of animal experimental study on lung transplantation field among countries/regions and institutions in 2004–2023. (A) Cooperative relationships between 39 countries/regions regarding animal experimental study on lung transplantation. (B) Cooperative relationships between 878 institutions connected to the animal experimental study on lung transplantation.

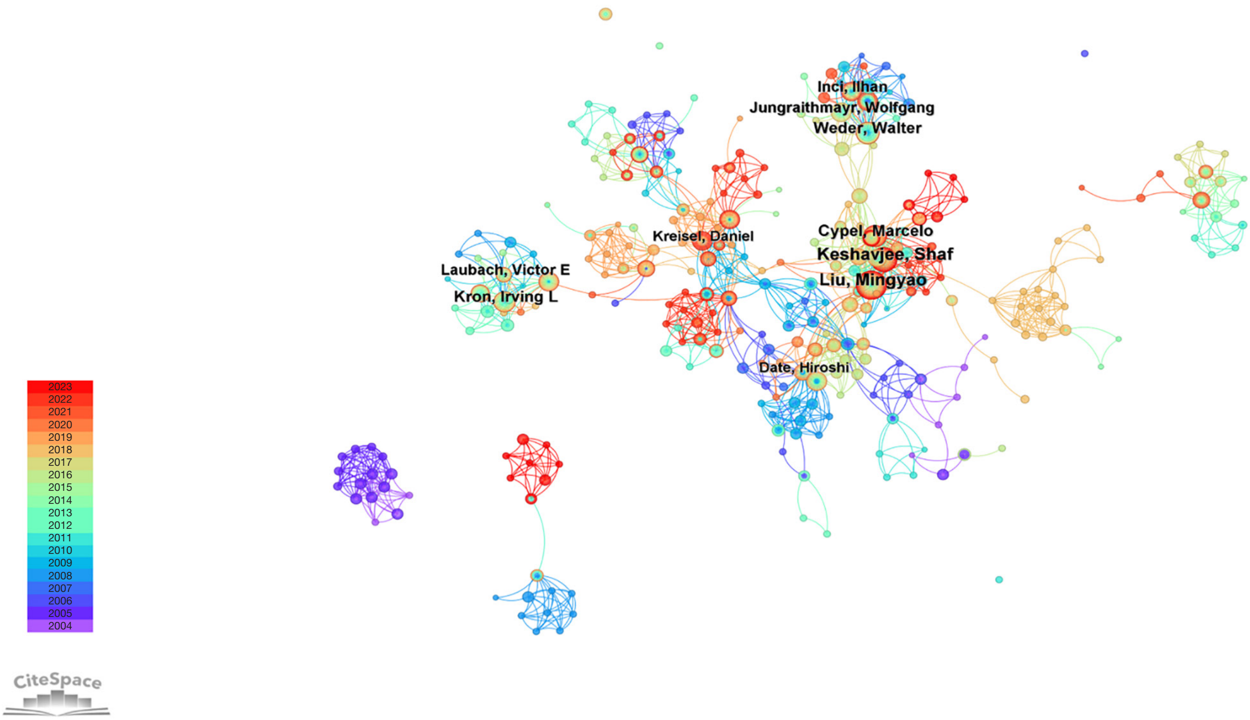


Figure 4 The CiteSpace network illustrates the authorship connections in animal experimental studies on lung transplantation, highlighting the top 10 authors with the most publications. Each circle represents an author, and the links between circles indicate collaboration between each other. The size of each circle corresponds to the number of articles published by a certain author.

of these, 9 journals came from USA, with the remaining one originating from The Netherlands. These journals primarily focused on transplantation or respiration. *Journal of Heart and Lung Transplantation* ranked first with 2,725 total citations, followed by *American Journal of Transplantation* (n=1,989) and *Journal of Thoracic and Cardiovascular Surgery* (n=1,322). Three journals had an impact factor (IF) exceeding 10, namely *Nature Medicine* (82.9), *American Journal of Respiratory and Critical Care Medicine* (25.7), and *Journal of Clinical Investigation* (15.9), respectively.

Analysis of highly cited articles

The number of citations is a crucial factor in determining the influence of an article within a particular research field. After counting and ranking the citations for 995 articles, the top 10 are displayed in *Table 3*. The article with the highest number of citations was published in 2010 by Ott *et al.* of Harvard University in the *Nature Medicine* (18), and it has been cited 838 times. This study delves into the process of regeneration and allotransplantation of a bioartificial lung, revealing that whole lung scaffolds created through decellularization perfusion can regenerate physiologically functional lung tissue and exhibit *in vivo* functionality post-transplantation.

Analysis of highly cited references, co-cited references and clustered network

Through the analysis of 995 articles and their 21,776 references (excluding self-citations), we have pinpointed the top 10 highly cited references in animal experimental research on lung transplantation from 2004 to 2023. These references are detailed in *Table 4*. The highest-ranking cited reference was a review published by *American Journal of Respiratory and Critical Care Medicine* in 2003 (19). This review delves into the intricate pathological mechanism of lung IR injury and highlights the potential to decrease the incidence of IR injury by enhancing lung protection techniques, developing new protective solutions, and implementing innovative protective and reperfusion strategies.

Table 2 The top 10 most active journals that published articles concerning animal experimental study on lung transplantation from 2004 to 2023 (sorted by total citation)

Rank	Journal	Total citations	Frequency	Average citation per paper	IF (2023)	JCR	Country
1	*Journal of Heart and Lung Transplantation*	2,725	118	23.09	8.9	Q1	USA
2	*American Journal of Transplantation*	1,989	55	36.16	8.7	Q1	USA
3	*Journal of Thoracic and Cardiovascular Surgery*	1,322	55	24.04	6	Q1	USA
4	*Transplantation*	1,184	69	17.16	6.2	Q2	USA
5	*Nature Medicine*	933	3	314	82.9	Q1	USA
6	*American Journal of Respiratory and Critical Care Medicine*	930	17	54.71	25.7	Q1	USA
7	*Journal of Immunology*	833	17	49	4.4	Q2	USA
8	*Annals of Thoracic Surgery*	807	33	24.45	4.6	Q2	The Netherlands
9	*Journal of Clinical Investigation*	714	14	51	15.9	Q1	USA
10	*Plos One*	495	28	17.68	3.7	Q2	USA

IF, impact factor; JCR, Journal Citation Reports.

References may indicate the subject matter of an article to some degree. Therefore, co-citation analysis is able to uncover the connection between two documents by identifying references that are co-cited in multiple publications. The visualization of co-cited references in *Figure 5A* showed a network with 891 nodes and 3,664 links. References with the top 25 burst strength among the 995 focusing on animal experimental research of lung transplantation from 2004 to 2023 are exhibited in *Figure 5B*. The green line represents the time span from 2004 to 2023, while the red line depicts a sudden rise in cited frequency for a specific reference during that same period. Over the past 20 years, references that garnered citation bursts usually revolved around synthesized reports from the ISHLT. These articles have been cited for their comprehensive and up-to-date information on lung transplantation, making them essential resources for researchers and practitioners in this field. Other primary focuses were on IR injury, PGD and OB. The latest reference burst occurred in 2021 and was a consensus report from the Pulmonary Council of the ISHLT published *by Journal of Heart and Lung Transplant* in 2019. This report primarily addressed the diagnostic criteria and treatment approaches for CLAD following lung transplantation (20). The strongest reference burst, which was also the top ranked cited reference in *Table 4*, occurred in 2004 and continued until the end of 2008, boasting a strength of 18.53.

In *Figure 6A*, co-cited references were categorized into 10 primary cluster labels, *ex-vivo* lung perfusion, EVLP, OB, necroptosis, bronchiolitis obliterans, non-heart-beating donor, donation after circulatory death (DCD), xenotransplantation, hydrogen sulfide and alveolar macrophage. Despite Cluster #0 and Cluster #1 sharing the same interpretation, their clustering times exhibit discrepancies (illustrated in *Figure 6B*), resulting in their separation in this study. There was an inverse relationship between the number of cluster labels and the number of articles within each cluster. Cluster #0 on EVLP, for example, had the highest number of papers compared to all other co-cited references.

The timeline depicted in *Figure 6B* showcases the evolution of separate co-citation clusters and emphasizes a transformation in the key areas of basic lung transplantation research through the last two decades. In the realm of animal experimental research for lung transplantation, the EVLP cluster and the DCD cluster stood out as the top two largest clusters. Necroptosis and EVLP were the most prevalent co-citation clusters observed in the latest research. Additionally, EVLP was the co-citation cluster with the longest duration, spanning from 2002 to 2023.

Analysis of research trend and burst detection with keywords

The word cloud in *Figure 7A* highlights the top 100 high frequency keywords in the field of animal experimental

Table 3 The top 10 most cited articles from 995 retrieved list concerning animal experimental study on lung transplantation from 2004 to 2023 (sorted by cited frequency)

Rank	Title	Cited frequency	First author	Journal	Year	IF	DOI
1	Regeneration and orthotopic transplantation of a bioartificial lung	838	Ott HC	*Nature Medicine*	2010	82.9	10.1038/nm.2193
2	Technique for Prolonged Normothermic Ex Vivo Lung Perfusion	387	Cypel M	*Journal of Heart and Lung Transplantation*	2008	8.9	10.1016/j.healun.2008.09.003
3	Metabolites released from apoptotic cells act as tissue messengers	263	Medina CB	*Nature*	2020	64.8	10.1038/s41586-020-2121-3
4	Normothermic Ex Vivo Perfusion Prevents Lung Injury Compared to Extended Cold Preservation for Transplantation	206	Cypel M	*American Journal of Transplantation*	2009	8.7	10.1111/j.1600-6143.2009.02775.x
5	Neutrophil Extracellular Traps Are Pathogenic in Primary Graft Dysfunction after Lung Transplantation	178	Sayah DM	*American Journal of Respiratory and Critical Care Medicine*	2015	25.7	10.1164/rccm.201406-1086OC
6	Interleukin-6/interleukin-21 signaling axis is critical in the pathogenesis of pulmonary arterial hypertension	172	Hashimoto-Kataoka T	*Proceedings of the National Academy of Sciences of the United States of America*	2015	11.1	10.1073/pnas.1424774112
7	Lung resident mesenchymal stem cells isolated from human lung allografts inhibit T cell proliferation via a soluble mediator	161	Jarvinen L	*Journal of Immunology*	2008	4.4	10.4049/jimmunol.181.6.4389
8	Enhanced In Vivo Function of Bioartificial Lungs in Rats	139	Song JJ	*Annals of Thoracic Surgery*	2011	4.6	10.1016/j.athoracsur.2011.05.018
9	Anti-type V collagen lymphocytes that express IL-17 and IL-23 induce rejection pathology in fresh and well-healed lung transplants	139	Yoshida S	*American Journal of Transplantation*	2006	8.7	10.1111/j.1600-6143.2006.01236.x
10	A mouse model of orthotopic vascularized aerated lung transplantation	138	Okazaki M	*American Journal of Transplantation*	2007	8.7	10.1111/j.1600-6143.2007.01819.x

IF, impact factor; DOI, digital object identifier.

research on lung transplantation over the past two decades. The size of the font positively indicates the frequency of each keyword. Following the elimination of keywords with little real significance or synonym, transplantation, expression, injury and model emerged as the used as the highest frequently keywords. The method of keywords burst detection can give an insight into a particular research area and capture current hotpots. Keywords lacking research significance were omitted, and instead, we identified the top 20 keywords with the strongest citation bursts in basic lung transplantation research publications from 2004 to 2023, as illustrated in *Figure 7B*. Between 2010 and 2018, mice emerged as the central topic in animal experimental research on lung transplantation, boasting the highest strength of 7.38. Since 2018, the latest keyword burst has been focused on lung IR injury, lung transplant, hypoxia and differentiation, although with relatively low burst strength up to this point.

Discussion

This study provides the initial bibliometric and visual analysis of animal experimental researches on lung

Table 4 The top 10 high cited references of 995 retrieved articles in the field of animal experimental research on lung transplantation from 2004 to 2023 (sorted by cited frequency)

Rank	First author	Cited references	Cited frequency	Journal	Year	DOI
1	de Perrot M	Ischemia-reperfusion-induced lung injury	42	*American Journal of Respiratory and Critical Care Medicine*	2003	10.1164/RCCM.200207-670SO
2	Stewart S	Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection	29	*Journal of Heart and Lung Transplantation*	2007	10.1016/J.HEALUN.2007.10.017
3	Cypel M	Normothermic ex vivo lung perfusion in clinical lung transplantation	28	*New England Journal of Medicine*	2011	10.1056/NEJMOA1014597
4	Okazaki M	A mouse model of orthotopic vascularized aerated lung transplantation	25	*American Journal of Transplantation*	2007	10.1111/J.1600-6143.2007.01819.X
5	Hertz MI	Reproduction of the obliterative bronchiolitis lesion after heterotopic transplantation of mouse airways	20	*American Journal of Pathology*	1993	None
6	Steen S	Transplantation of lungs from a non-heart-beating donor	20	*Lancet*	2001	10.1016/S0140-6736(00)04195-7
7	Mizuta T	Simplified rat lung transplantation using a cuff technique	20	*Journal of Thoracic and Cardiovascular Surgery*	1989	None
8	Fiser SM	Ischemia-reperfusion injury after lung transplantation increases risk of late bronchiolitis obliterans syndrome	19	*Annals of Thoracic Surgery*	2002	10.1016/S0003-4975(01)03606-2
9	den Hengst WA	Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process	19	*American Journal of Physiology-Heart and Circulatory Physiology*	2010	10.1152/AJPHEART.00251.2010
10	Cypel M	Technique for prolonged normothermic ex vivo lung perfusion	17	*Journal of Heart and Lung Transplantation*	2008	10.1016/J.HEALUN.2008.09.003

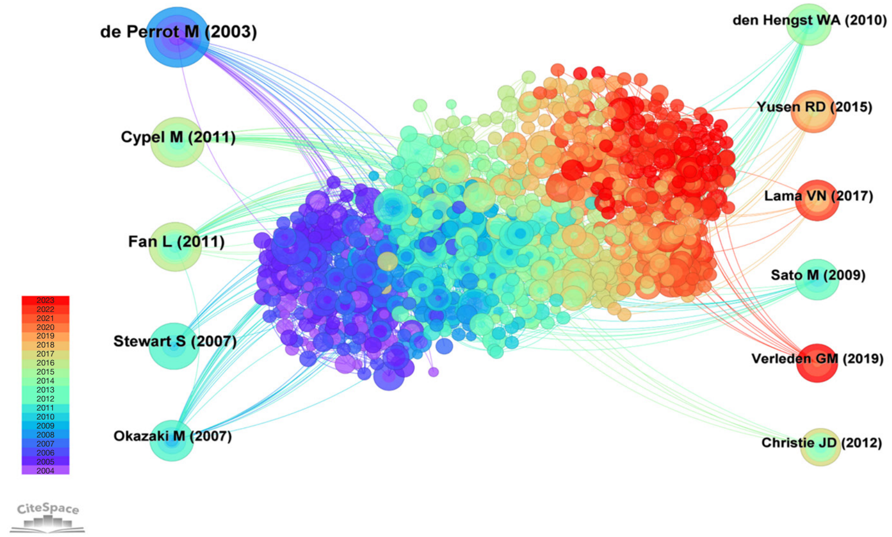
The number of cited frequency means the how many of the 995 articles cited this one as reference. For instance, "42" means that there are 42 publications in the 995 articles cited "Ischemia-reperfusion-induced lung injury" as one of references. DOI, digital object identifier.

transplantation from 2004 to 2023. By identifying the animal models, research trends and hotspots in basic lung transplantation research, our analysis provides valuable insights for researchers and may guide future studies in this area.

Overall trends in the field of animal experimental research on lung transplantation

Our analysis reveals a substantial global interest in basic research on lung transplantation. According to a recent bibliometric analysis by Tokur *et al.* (21), a total of 10,467 publications had been made on lung transplantation between 1983 and 2021. However, their analysis did not separate basic studies and clinical studies and did not investigate overall trends and hotspots. Our present analysis revealed that the use of animal models in lung transplantation research has been steadily increased over the past 20 years. This is in line with the increasing trend of animal experimentation in biomedical research as a whole. Animal models play a crucial role in understanding the underlying mechanisms of complications after lung transplantation and developing new treatment strategies (15,22,23). When comparing to mice, rats are larger and easier to operate, making them the most commonly used animals for orthotopic lung transplantation research. However, our analysis also identified an increase in the

A



B

Top 25 references with the strongest citation bursts				
References	Strength	Begin	End	2004–2023
Verleden GM, 2019, J HEART LUNG TRANSPL, V38, P493, DOI 10.1016/i.healun.2019.03.009, DOI	9.42	2021	2023	
Yusen RD, 2016, J HEART LUNG TRANSPL, V35, P1170, DOI 10.1016/i.healun.2016.09.001, DOI	6.52	2019	2020	
Lama VN, 2017, JCI INSIGHT, V2, PO, DOI 10.1172/ici.insight.93121, DOI	8.32	2018	2023	
Laubach VE, 2016, CURR OPIN ORGAN TRAN, V21, P246, DOI 10.1097/MOT.0000000000000304, DOI	6.31	2018	2021	
Yusen RD, 2015, J HEART LUNG TRANSPL, V34, P1264, DOI 10.1016/i.healun.2015.08.014, DOI	9.71	2017	2020	
Yusen RD, 2014, J HEART LUNG TRANSPL, V33, P1009, DOI 10.1016/i.healun.2014.08.004, DOI	8	2016	2018	
Shiling RA, 2011, SEMIN IMMUNOPATHOL, V33, P129, DOI 10.1007/s00281-011-0257-9, DOI	6.25	2014	2016	
Fan L, 2011, AM JTRANSPLANT, V11, P911, DOI 10.1111/.1600-6143.2011.03482.x, DOI	12.49	2012	2016	
Cypel M, 2011, NEW ENGL J MED, V364, P1431, DOI 10.1056/NEJMoa1014597, DOI	12.94	2012	2016	
den Hengst WA, 2010, AM J PHYSIOL-HEARTC, V299, PH1283, DOI 10.1152/aipheart.00251.2010, DOI	9.99	2012	2015	
Christie JD, 2011, J HEART LUNG TRANSPL, V30, P1104, DOI 10.1016/i.healun.2011.08.004, DOI	8.07	2012	2014	
Christie JD, 2010, J HEART LUNG TRANSPL, V29, P1104, DOI 10.1016/i.healun.2010.08.004, DOI	6.97	2011	2015	
Sato M, 2009, AM JTRANSPLANT, V9, P1981, DOI 10.1111/.1600-6143.2009.02770.x, DOI	9.68	2011	2013	
Jungraithmayr WM, 2009, JTHORAC CARDIOV SUR, V137, P486, DOI 10.1016/j.jtcvs.2008.10.007, DOI	7.19	2010	2013	
Christie JD, 2008, J HEART LUNG TRANSPL, V27, P957, DOI 10.1016/i.healun.2008.07.018, DOI	8.12	2009	2012	
Stewart S, 2007, J HEART LUNG TRANSPL, V26, P1229, DOI 10.1016/.healun.2007.10.017, DOI	12.75	2009	2012	
Daud SA, 2007, AM JRESP CRIT CARE, V175, P507, DOI 10.1164/rccm.200608-10790C, DOI	6.89	2008	2012	
OkazakiM, 2007, AM JTRANSPLANT, V7, P1672, DOI 10.1111/.1600-6143.2007.01819.x, DOI	9.21	2008	2012	
TrulOCK EP, 2007, JHEART LUNG TRANSPL, V26, P782, DOI 10.1016/i.healun.2007.06.003, DOI	8.3	2008	2011	
Zhao MQ, 2006, AM JPHYSIOL-LUNG C, V291, PL1018, DOI 10.1152/ajplung.00086.2006, DOI	6.97	2008	2010	
Trulock EP, 2006, JHEART LUNG TRANSPL, V25, P880, DOI 10.1016/i.healun.2006.06.001, DOI	8.56	2007	2009	
TrulOck EP, 2005, J HEART LUNG TRANSPL, V24, P956, DOI 10.1016/.healun.2005.05.019, DOI	7.59	2006	2007	
de Perrot M, 2003, AM JRESP CRIT CARE, V167, P490, DOI 10.1164/rccm.200207-670S0, DOI	18.46	2004	2008	
Estenne M, 2002, AM JRESP CRIT CARE, V166, P440, DOI 10.1164/rccm.200201-003PP, DOI	6.75	2004	2007	
Steen S, 2001, LANCET, V357, P825, DOI 10.1016/S0140-6736(00)04195-7, DOI	7.84	2004	2006	

Figure 5 Reference co-citation network analysis of animal experimental study on lung transplantation between 2004 and 2023. (A) CiteSpace co-citation map of 21,776 references on basic lung transplantation study, filter option showing the largest connected component only. Each node within the retrieved 995 articles represents a reference, and the links between nodes indicate that these articles are cited as references in the same article. The size of the node is proportional to the frequency of citation, and the thickness of the line indicates the correlation with the co-cited papers. The top 11 authors with the most cited publications are listed with the last two were parallel. (B) Reference with the strongest burst strength of the 995 citing articles on basic lung transplantation study between 2004 and 2023. Reference marked in red indicates a sudden increase in usage frequency during the period, blue represents a relatively unpopular time period.

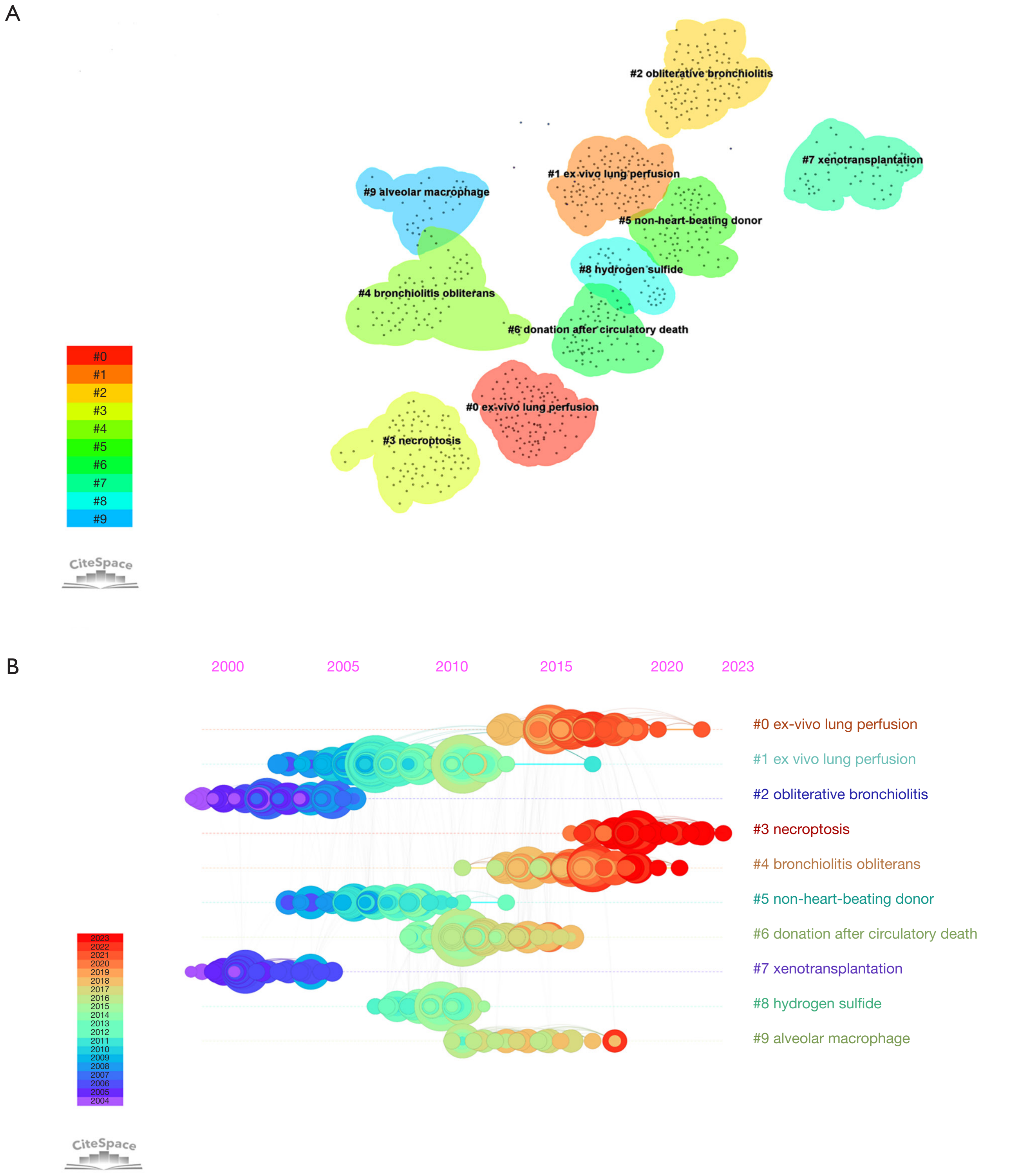


Figure 6 Analysis of co-occurring keywords of publications on animal experimental study for lung transplantation from 2004 to 2023. (A) Clustered networks of co-citation status of the investigated reference and the 995 citing articles using CiteSpace. The top 10 largest clusters of citing articles are shown. (B) A timeline view of the top 10 largest clusters of citing papers on the field of animal experimental study for lung transplantation.

A

B

Top 20 keywords with the strongest citation bursts				
Keywords	Strength	Begin	End	2004–2023
Lung ischemia-reperfusion injury	3.76	2021	2023	
Lung transplant	4.97	2020	2023	
Hypoxia	3.79	2020	2021	
Differentiation	6.1	2018	2023	
Animal models	4.9	2017	2020	
Stromal cells	4.13	2017	2019	
Mesenchymal stem cells	5.15	2017	2018	
Donor lungs	4.63	2015	2018	
Heart beating donors	4.89	2011	2015	
Obliterative bronchiolitis	4.15	2011	2013	
Mice	7.34	2010	2018	
TNF α	4.1	2009	2014	
In vivo	4.9	2009	2013	
Gene expression	3.84	2009	2012	
Nitric oxide	4.31	2008	2015	
Bronchiolitis obliterans	4.15	2008	2009	
Allograft rejection	6.86	2007	2010	
Rat	3.72	2004	2013	
Reperfusion injury	4.45	2004	2006	
Up regulation	4.86	2004	2006	

Figure 7 Analysis of keywords and burst detection of publications in the field of animal experimental research on lung transplantation between 2004 and 2023. (A) Word cloud generated using the R package bibliometrix to display the top 100 high-frequency keywords regarding animal experimental research on lung transplantation. (B) Keywords with the strongest burst strength of the 995 citing articles regarding animal experimental research on lung transplantation between 2004 and 2023. Keyword marked in red indicates a sudden increase in usage frequency during that period while blue represents a relatively unpopular time period.

number of orthotopic lung transplantations conducted on mice in recent years. One reason for this is that mice share genetic similarities with humans and possess short breeding cycles (24-27). Furthermore, the advancements in surgical techniques, along with the unremitting endeavors of scholars, have made the mouse model for orthotopic lung transplantation successful and replicable. Due to the effective utilization of gene knockout technology in mice, an increasing number of research has selected mice as models for delving into or confirming more intricate details. The broad range of species also makes heterotopic tracheal transplantation in mice a popular choice for studying chronic rejection, including OB. Besides, rat models still hold high value in certain areas of lung transplantation research, such as chronic rejection and IR injury. Because of the comparable lung anatomy and physiology to humans, swine are frequently used as the primary model for evaluating the effectiveness and safety of EVLP techniques. Nevertheless, recent advancements in technology have also made it possible to use smaller animal models, such as rats and mouse, for EVLP research (28,29). All these results clearly demonstrate the continuous dedication of researchers in the fundamental examination of lung transplantation. In general, the continued use and advancement of animal models, particularly mice, in basic lung transplantation research is essential for further understanding and improving the outcomes of lung transplant patients.

The USA has always been the primary country involved in animal experimental research on lung transplantation for the past two decades, leading in the total number of publications. This is not surprising, as the USA has been a leader in lung transplantation and has the high number of lung transplant centers in the world. Additionally, the USA possesses a strong research infrastructure and ample funding opportunities for biomedical research, as well as the closest collaboration with other countries. Due to its top average citations, as well as the institutions and authors involved, Canada has played a crucial role in advancing basic research in lung transplantation. Canadian scientists have successfully implemented EVLP, a technique that has been widely embraced and holds great importance in the field of lung transplantation. Furthermore, Canadian researchers have a strong commitment to enhancing the quality of EVLP, and mitigating complications such as reperfusion injury and postoperative rejection (30,31). Currently in Toronto, Canada, the EVLP system is capable of conducting 12 hours of *in vitro* perfusion preservation, evaluating uncontrolled DCD donors, and investigating different donor lung repair techniques, such as *in vitro* anti-infection, antiviral therapy, and gene therapy using the EVLP platform. This has led to an enhancement in the utilization rate of donor lungs (32). The EVLP system is now grappling with issues like high operational costs and delays in lung maintenance time, which are obstacles that Canadian scientists and many others are working to resolve. As a result, Canada has become a key player in the global effort to improve outcomes for lung transplant patients. Besides, Japan and China have also demonstrated significant involvement in basic lung transplantation research. The survival rates for lung transplantation in Japan are currently reported to be approximately 73% at 5 years and 60% at 10 years. The outcomes of lung transplantation in Japan seem to be relatively favorable when compared to international registry data, which indicates a 5- and 10-year survival rate of approximately 55–60% and 35–40% (33). Undoubtedly, advancements in donor lung preservation, surgical techniques and immunosuppression therapy have played a significant role in the higher number of long-term survivors after lung transplantation in Japan (34). Thoracic surgeons in Japan are vigorously engaged in both performing surgeries and managing postoperative care in the intensive care unit (ICU), with or without the presence of intensivists. This intensive involvement and specialized attention could be a contributing factor to the positive outcomes observed in Japan. However, Japan's success can also be attributed to the relatively low number of lung transplantations performed in the country, with only around 1,000 cases recorded in the last 20 years. Due to the requirement for lifelong immunosuppression, individuals who survive long-term after lung transplantation are at risk for late complications, like CLAD, OB, infection and chronic kidney disease (CKD). In Japan, researchers are conducting fundamental studies on lung transplantation, with a primary focus on utilizing animal models to improve the functionality of donor lungs and reduce postoperative complications such as CLAD and OB. Though the number of publications in Japan and China was comparable at present, it appears that China may soon exceed Japan in terms of the number of publications, as indicated by a higher number of articles published from China since 2015. There are two possible reasons for the increase of publications of China in recent years. Firstly, the traditional Confucianist belief in China, which emphasizes keeping the bodies of the deceased intact, is becoming less prevalent as economic and social development advanced (35). Numerous large-scale social surveys have indicated that China possesses a large pool of potentially suitable donor organs (36,37). This has led to an increase in the number of lung transplant surgeries and consequently, a greater need for both clinical and basic research on the topic. Secondly, the initiation of a pilot program for organ DCD in China in 2012 (36) also resulted in the development of a sustainable organ transplantation system and expanded the opportunities for DCD experiments in both human and animal models (38).

Prior research focus on experimental research in lung transplantation

Unlike the extensive cooperation among countries or institutions, productive authors may prefer for stable partnerships in the field of basic lung transplantation research. In the past 20 years, Keshavjee Shaf and Mingyao Liu, both affiliated with the University of Toronto, were the most productive authors. They completed the first clinical trial of EVLP in 2011 and found that it had excellent outcomes in preventing ongoing injury caused by prolonged ischemia and accelerates lung recovery (32). This study had a profound impact on the lung transplantation community. Additionally, they have demonstrated that *ex vivo* treatment enhances post-transplant lung function compared to EVLP alone (39,40). These endeavors could greatly improve lung transplantation outcomes. Furthermore, Shaf Keshavjee and Mingyao Liu also served as guest professors at the Lung Transplantation Center in Wuxi, China, indicating an international collaboration in the field of lung transplantation.

The top 10 most cited references typically cover a range of topics related to animal experimental research on lung transplantation, providing important resources for researchers in the field. Overall, the co-citation cluster progressing in this field underscores the persistent endeavors to address the challenges and improve outcomes in lung transplantation through innovative techniques and a more profound comprehension of the underlying mechanisms involved. The timeline of references with the clusters showed that EVLP and DCD are the strongest clusters. These two approaches have been developed to address the critical mismatch between the supply of donor lungs and the demand for clinical transplantation. DCD donors make up a substantial portion of the donor pool. For instance, during the period of 2011 to 2012, a total of 1,088 organ donors were recorded in the UK, with 436 of them being DCD donors (41). Nevertheless, it is indisputable that lungs donated after DCD are frequently the most challenging 'marginal' donor lungs to evaluate. EVLP has shown great promise in identifying suitable DCD lungs for transplantation. By utilizing EVLP, it is possible to transform unusable or extended criteria grafts into viable transplantable grafts or grafts with a lower likelihood of posttransplant issues through innovative methods such as gene modification, bioengineering, regeneration and scaffolding (42). This technique has been adopted globally and has led to a significant rise in the availability of transplantable lungs by at least 15–20% (43).

Various forms of cell death associated with acute lung injury have been observed in both cellular and animal models, as well as in clinical studies of lung transplant (6,44,45). The latest prevalent co-citation cluster, necroptosis, a nonapoptotic form of cell death, triggers the recruitment of neutrophils during lung ischemia and reperfusion (46). Inhibiting necroptosis has been proven to reduce IR injury in rodent models of lung transplantation (47,48). According to Wang and colleagues' study (49), targeting necroptotic cell death could be a crucial strategy in preventing PGD following lung transplantation, especially when combined with interventions aimed at improving the condition of donor lungs before engraftment. This highlights the importance of better understanding the multiple types of cell death especially necroptosis in the area of lung transplantation and the potential for targeted interventions to improve outcomes. Although both EVLP and necroptosis inhibition were implemented to enhance the condition of the donor lungs, there is a lack of published research investigating the relationship between the two. This gap in knowledge could open up a new area of basic research in the field of lung transplantation. Further studies exploring the potential synergistic effects of EVLP and necroptosis inhibition might provide valuable insights into improving lung transplant outcomes and reducing the incidence of PGD.

Hotspots and emerging trends in basic lung transplantation research

In the last two decades, the most cited reference and strongest citation burst keyword point to lung IR injury as a perennial hotspot in lung transplantation. Lung IR injury is a main factor in causing PGD and contributing to long-term graft failure (48). IR injury typically occurs as a result of reactive oxygen species formation, leading to innate immune system activation, cytokine increase, and DAMPs (5). This immune activation triggers endothelial barrier dysfunction, ultimately causing edema, diffuse alveolar damage and hypoxemia. Despite extensive research efforts, many questions surrounding the mechanisms of lung IR injury remain unanswered. Therefore, it is expected that lung IR injury will continue to be a prominent topic in basic lung transplantation research in the coming years.

Since 2018, there has been a shift in focus towards hypoxia. This indicates that these topics are still emerging and have the potential to become significant areas of study in the future. Hypoxia often occurs in lung transplant recipients, and it is a key diagnostic marker for PGD grade. The main cause of hypoxia during lung transplantation is primarily caused by abnormal vasculature. Initially, hypoxia is a result of organ procurement, involving necessary ischemia that can result in IR injury (50). Later on, hypoxia may occur due to the loss of micro-vessels during episodes of alloimmune rejection, resulting in vascular injury and significant regional tissue ischemia, ultimately leading to CLAD (51). Numerous strategies have been shown to be effective in reducing hypoxia and improving outcomes, including applying iron chelators to the anastomosis site at the time of surgery (52), implementing a short period of anti-coagulation (53), stimulating angiogenesis (54), enhancing oxygen delivery, and more. However, additional practices were required to validate these findings. Hence, further exploration in this area is necessary to advance our comprehension and establish efficient interventions for hypoxia in lung transplantation.

Besides hypoxia, differentiation is another hotspot topic in basic lung transplantation research. This reflects an increasing enthusiasm for utilizing stem cells and regenerative medicine to tackle challenges in lung transplantation. Differentiation in lung transplantation involves cells becoming specialized and acquiring specific functions, which is essential for repairing damaged tissue and promoting lung regeneration. The advancement in cellular and biotechnologies provides a new solution, suggesting the utilization of lung organoids for patients in need of lung transplants (55). Progress in this area could expand potential therapeutic targets for alveolar regeneration, offering options beyond lung transplantation, and aiding in the creation of successful therapeutic approaches that stimulate or replenish stem cells in the lung. This could potentially lead to improved outcomes for lung transplant recipients and alleviate the shortage of suitable donor organs. In brief, the recent burst of keywords suggests that researchers are focusing on exploring the mechanisms of IR injury in lung transplantation and seeking new ways to improve outcomes of lung transplant.

Limitations and future directions

There are some limitations in our analysis. Firstly, our analysis was restricted to articles published in the WoSCC, which may not fully represent publications in the field of animal experimental research on lung transplantation. Nevertheless, the data from WoSCC contained comprehensive information necessary for bibliometric analysis, including title, author, institute, and reference. Secondly, the search strategy of our study, including restrictions on publication language and types, might have led to the exclusion of some articles that could have been significant. Furthermore, despite the recent increase in the number of articles published in the field, the overall quantity is still relatively low. As a result, our analysis may be somewhat biased due to the limited literature available. Future studies could expand on our analysis by including a wider range of databases and languages to provide a more comprehensive overview of animal experimental research on lung transplantation. Incorporating qualitative analysis and expert opinions could also provide a deeper understanding of the current trends and hotspots in this field.

Conclusions

Through the assistance a bibliometric tool, we have summarized and evaluated publications in the field of animal experimental research on lung transplantation from 2004 to 2023. Rats, mice, and swine are the most commonly used animal models for basic lung transplantation research. The most frequently employed model of lung transplantation in animals includes orthotopic lung transplantation, IR, and EVLP. The most commonly used animal models for basic lung transplantation researches were rats and mice. USA, Canada, Japan and China were the leading contributors to this area. The top cited references indicate a strong focus on utilizing EVLP and DCD techniques to expand donor availability since 2010. The recent keyword bursts demonstrate the ongoing efforts to addressing post-transplant complications such as lung IR injury and hypoxia, and develop effective treatments. Further investigation into the potential synergistic effects of combining EVLP with necroptosis inhibition may provide valuable insights to enhance lung transplant outcomes. Overall, our analysis provides a comprehensive overview of the current state of animal experimental research on lung transplantation during the past two decades, evaluating current publication trends and focal points and offers significant insights for current research endeavors.

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Footnote

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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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