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Original Article

Publication trends of research on acute lung injury and acute respiration distress syndrome during 2009-2019: a 10-year bibliometric analysis

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Abstract: Background: Acute lung injury (ALI) is a common disease that usually progresses to acute respiratory distress syndrome (ARDS) with high morbidity and mortality. We aim to analyze the trends in ALI/ARDS, and to compare the differences in aspects of years, countries, institutions, journals, etc. Methods: We screened all relevant literature on ALI/ARDS from Web of Science during 2009-2019, and analyzed the research trends in this field by VOSviewer. Results: We had screened 7,890 publications with a total cited frequency of 164,713. The United States contributed the largest number of publications (2,612, 33.11%), cited frequency (81,376, 48.61%), and the highest H-index (107). *Journal of Critical Care Medicine* published the largest number of literatures on ALI/ARDS, MATTHAY MA published the majority of articles in this field (147), while SLUTSKY AS received the most cited frequency (10015). University of California San Francisco had the largest number of publications (243, 3.08%) among all full-time institutions. In the aspect of clinical research in ALI/ARDS, the keyword "Berlin definition" emerged in recent years, with an average year of 2016.3; in the basic research, the key word "protects" appeared latest, and the average years were 2016.5. The current research trend indicates that basic research is gradually transforming into clinical research. Conclusions: The United States have made the most significant contribution to the ALI/ARDS field in the last decade. The current research 'hotspot' mainly appeared in clinical research, such as "Berlin definition". In regards to basic research, studies tend to explore the protective mechanisms against ALI/ARDS.

Keywords: Bibliometrics, publication, ALI, ARDS, lung

Introduction

Acute lung injury (ALI) is a severe lung injury caused by variety of direct or indirect factors, and often progresses to acute respiratory distress syndrome (ARDS) [1, 2]. The typical pathological and physiological characteristics of ALI include decreased lung volume, reduced lung compliance and low ventilation/blood flow ratio [3], with notably high morbidity and mortality [4]. In 2005, the morbidity of ALI in the United States is 78.9/100,000 and the mortality rate is 38.5% [5]. At the end of 2019, a novel coronavirus-infected pneumonia has spread quickly in China. According to newest report on the clinical characteristics of 138 hospitalized patients in Wuhan, China, 36 patients were transferred to the intensive care unit (ICU) because of complications, among them the most common complication was ARDS (22 [61.1%]) [6].

Causes of ALI include pulmonary factors (direct injuries) and extrapulmonary factors (indirect injuries). Traditional treatment for ALI/ARDS includes the control of primary disease, inflammatory reaction inhibition, respiratory support, fluid management, hormone therapy, etc [7]. In recent years, in the help of research, growing number of studies have confirmed the effectiveness of intervention measures. Drug treatments reduce lung injury by regulation of signal pathways. For instances, p-coumaric acid alleviates LPS-induced lung injury in rats by scavenging ROS [8], and protein Kinase C can reduce

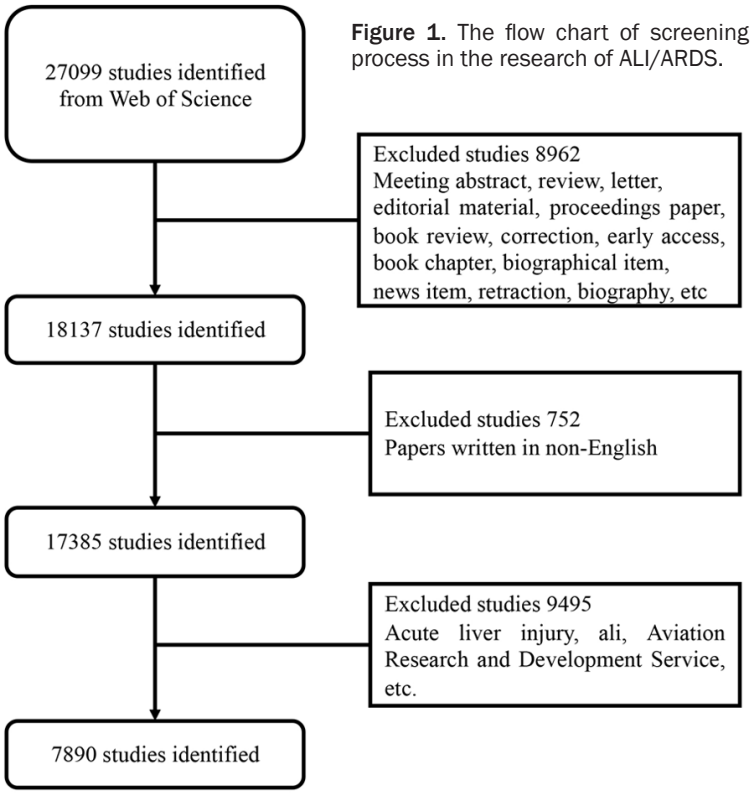


Figure 1. The flow chart of screening process in the research of ALI/ARDS.

LPS-induced lung injury in mice via the Notch Signaling Pathway by suppressing Th17 cell response [9], and resveratrol inhibits neutrophil activation and Src family kinases activity thereby alleviating lung injury [10]. The current research mainly focuses on the animal studies or preclinical work, and there are no clear or effective illustrations of treatment strategy for ALI. To explore the potential targets, we tried to review the recent research trends and predict the potential future hotspot.

Bibliometric analysis is often used to indicate the trend of time changes in a certain research field, and make qualitative and quantitative analysis of scientific journals and books, contributing greatly to disease treatment and the development of clinical guidelines [11-13]. Besides, the advantage of bibliometrics is not only a reflection on publishing trends, but also an indication for the future research hotspots. It has been widely used in the current medical research such as sepsis [14], osteoarthritis [15] and cancer [16]. In this study, we conducted bibliometric to analyze the ALI/ARDS based on Web of Science (WOS), to clarify the research progress and trend nowadays and speculate the future hotspots of ALI/ARDS.

Materials and methods

Data sources and search strategies

We made use of the Web of Science which is widely accepted in bibliometric analysis, to conduct a comprehensive online search on ALI/ARDS from 2009 to 2019. All data were collected online and no ethical proof was required. All searches were conducted on November 27, 2019 to avoid bias of database renewal. The search strategies were shown as follows, TS: ("acute lung injury") OR TS: ("acute lung injuries") OR TS: ("acute lungs injury") OR TS: ("acute lungs injuries") OR TS: (ALI) OR theme: (ARDS) OR TS: ("acute respiratory distress syndrome") OR TS: ("acute respiratory distress syndromes") AND language: (English). Furthermore, peer-reviewed articles were reserved, and all other categories were excluded. The screening process is shown in **Figure 1**.

Data collection

Two authors (CW and XRW) independently extracted all data from included articles, including titles, keywords, authors, institutions, journals, dates of publication, countries/regions, citations, H-index, etc. Then we analyzed the data using GraphPad Prism 6 and VOSviewer.

Bibliometric analysis

We used the WOS to describe the characteristics of included publications. The relative research interest (RRI) was defined by the number of publications associated with a particular research field, and then was divided by the number of publications per year in all fields [17, 18]. The impact factor (IF) was acquired in the newest edition of the journal citation report (JCR). H-index, which widely accepted as a reflection of research influence among scientists or countries, means scientists or countri-

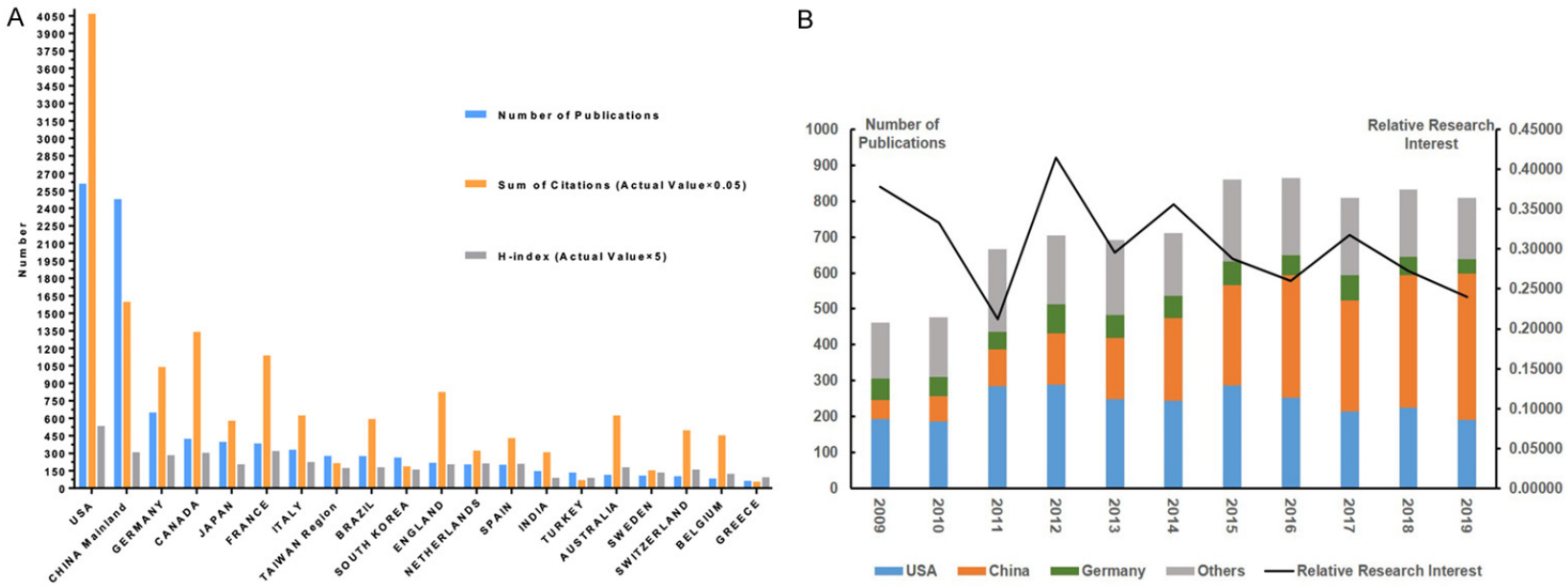


Figure 2. Articles related to ALI/ARDS published worldwide. A. The number of publications, citation frequency (actual value × 0.05), and H-index (actual value × 5) in the top 20 countries or regions; B. The annual publications worldwide and in top 3 countries, and the relative research interest of ALI/ARDS. Polyline represents the relative research interest every year.

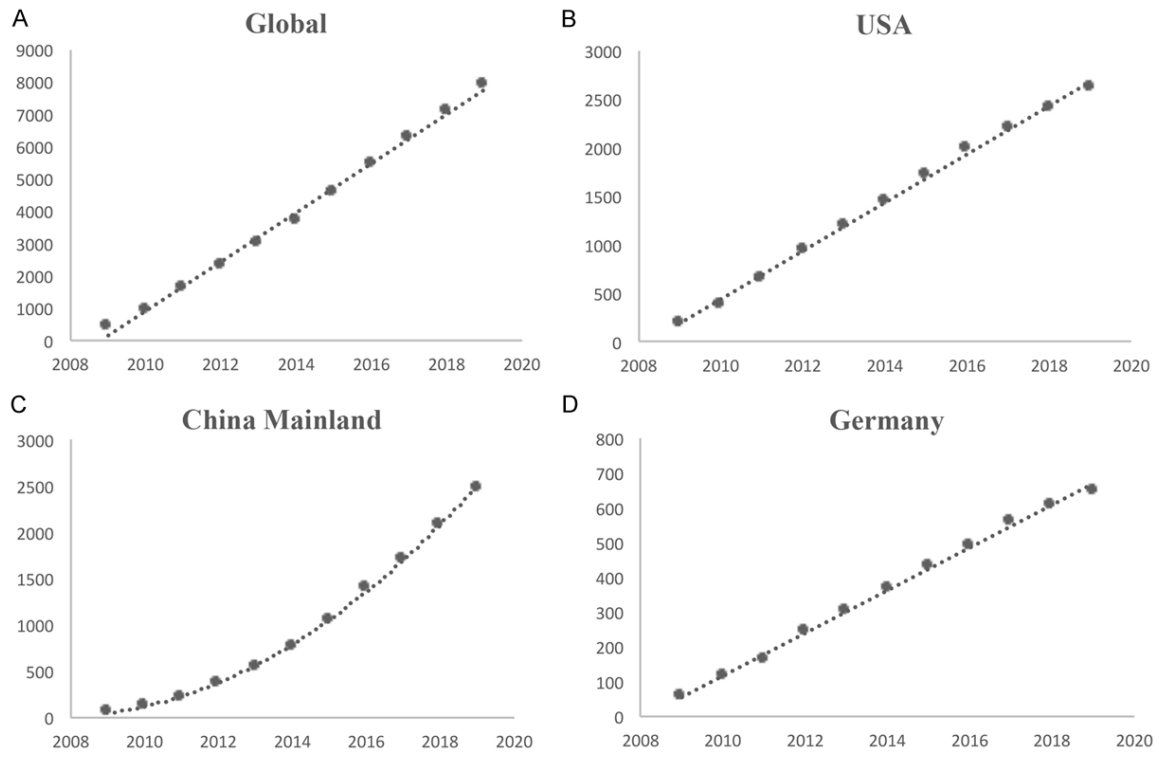


Figure 3. The trend of annual publications related to ALI/ARDS among worldwide and top 3 countries. A. Global; B. USA; C. China Mainland; D. Germany.

es have published "H" papers and the papers have been cited in other publications for at least "H" times [19, 20].

The relationship between highly cited references and prolific authors was analyzed using VOSviewer software, which maps the network of keywords which associate with ALI/ARDS and classifies keywords into several clusters with colors according to the co-occurrence times. The average appearing year (AAY) was used to describe the relative novelty of keywords [21].

Results

Global contribution to publications on ALI/ARDS

Referred to the inclusion criteria, 7,890 articles related to ALI/ARDS were included in our study. The ranking of the origin of those publications are as listed: first, USA (2,612, 15.02%); second, China (2,480, 14.27%); third, Germany (650, 3.74%); fourth, Canada (424, 2.44%); fifth, Japan (397, 2.28%). According to the annual number of publications, the largest number appeared in 2016 (only period from January to November were counted in 2019 and the data were not taken into account in the ranking) (**Figure 2A**). By calculating the RRI value, we found in the year 2012 there are the highest number of publications related to ALI/ARDS (**Figure 2B**). As for the contribution from each nation, in 2009 the articles from China was considerably less than from the United States, but in 2016, China began to surpass the United States, ranking first in the number of publication.

Citations and H-index analysis

We analyzed the screened publications from 2009 to 2019 through Web of Science as shown above. All publications related to ALI/ARDS were cited 164713 times (excluding self-citation, 128862), with an average of 20.88 times per article. The United States ranked the first, with 49.40 percent, 81,376 citations (excluding self-citation 73108), and the H-index was 107. The second most-cited country was China, 31996 (excluding self-citation, 26075), and the H-index was 62. Germany ranked the

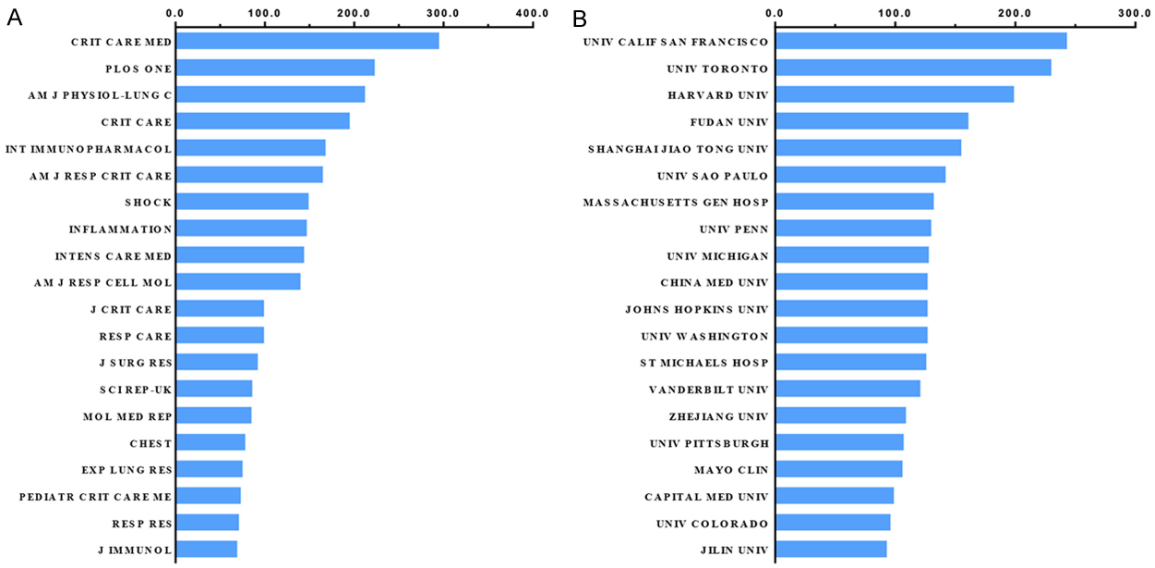


Figure 4. Articles published in different journals and institutions on ALI/ARDS. A. The top 20 journals by the amount of publications related to ALI/ARDS; B. The top 20 institutions categorized by the amount of publications related to ALI/ARDS.

third, although there were only 650 publications, it contributed 20,797 citations (excluding self-citation, 19846), with H-index of 57 (**Figure 2A**).

Growth trend of publications

To visualize the cumulative volume of global and country publications, we plotted the growth curve in **Figure 3**. We found that, except for China, the volume of publications among global, USA and Germany were linearly correlated (**Figure 3A**, **3B** and **3D**). China, in contrast, showed an exponential growth, which has been gradually climbing since 2016 (**Figure 3C**).

Journals publishing researches on ALI/ARDS

The top 20 journals accounted for 30.14% (2665) of all publications on ALI/ARDS. Specifically, Critical Care Medicine (IF 6.97) ranked the first with 295 publications, and PLOS ONE with 223 articles went after. And, American Journal of Physiology Lung Cellular and Molecular Physiology (IF 4.06), Critical Care (IF 6.96) and International Immunopharmacology (IF 3.36) ranked third, fourth and fifth place, respectively, with the total number of 212/195/168. The number of publications ranked the fifth and the tenth showed a mild drop, from 168 to 140. The top 20 journals were listed in **Figure 4A**.

Institutions publishing researches on ALI/ARDS

University of California San Francisco in the United States had the largest number of publications among all full-time institutions, with 243 publications, accounting for 3.08% of the total. The second, Toronto University in Canada, produced 230 publications, accounting for 2.92% of the total. The Harvard University in the US ranked the third with 199 publications, accounting for 2.52%. Among the top 20 institutions, majority (11) of institutions are from the United States, followed by China and Canada, with 6 and 2 institutions respectively, and Brazil with 1 institution ranked the forth. The top 20 journals published the most papers were listed in **Figure 4A** and **4B**.

Authors publishing researches on ALI/ARDS

All the top 10 authors contributed a total number of 799 publications, which takes 10.13% of the total. MATTHAY MA (Univ Calif San Francisco) ranked the first with 147 publications, followed by WANG Y (Zhejiang Univ) and ZHANG Y (Cent S Univ) from China, with 81 and 79 articles, respectively. Among the top 10 authors, there are 4 Americans, 3 Chinese, 2 Canadians and 1 Italian. Details are showed in **Table 1**.

In the rankings of reference quantity, the Acute Respiratory Distress Syndrome, the Berlin

Table 1. Top 10 authors with most publications in research scope of acute lung injury

Author	Country	Affiliation	No. of Publications	No. of Citations
MATTHAY MA	USA	Univ Calif San Francisco, Med Ctr Parnassus, Dept Med	147	8444
WANG Y	CHINA Mainland	Zhejiang Univ, Coll Pharmaceut Sci	81	1429
ZHANG Y	CHINA Mainland	Cent S Univ, Subei Peoples Hosp Jiangsu Prov	79	1453
PELOSI P	Italy	Univ Genoa, IRCCS San Martino Ist Nazl Ric Canc	76	1846
LI Y	CHINA Mainland	Liaoning Canc Hosp & Inst, Dept Gen Surg	75	1589
CALFEE CS	USA	Univ Calif San Francisco, Dept Med	73	3084
THOMPSON BT	Canada	Univ Toronto, Interdept Div Crit Care Med	72	9102
GAJIC O	USA	Mayo Clin	68	4601
WARE LB	USA	Vanderbilt Univ, Med Ctr, Dept Med	65	3004
SLUTSKY AS	Canada	Univ Toronto	63	10015

Table 2. Top 10 high-cited papers related to acute lung injury

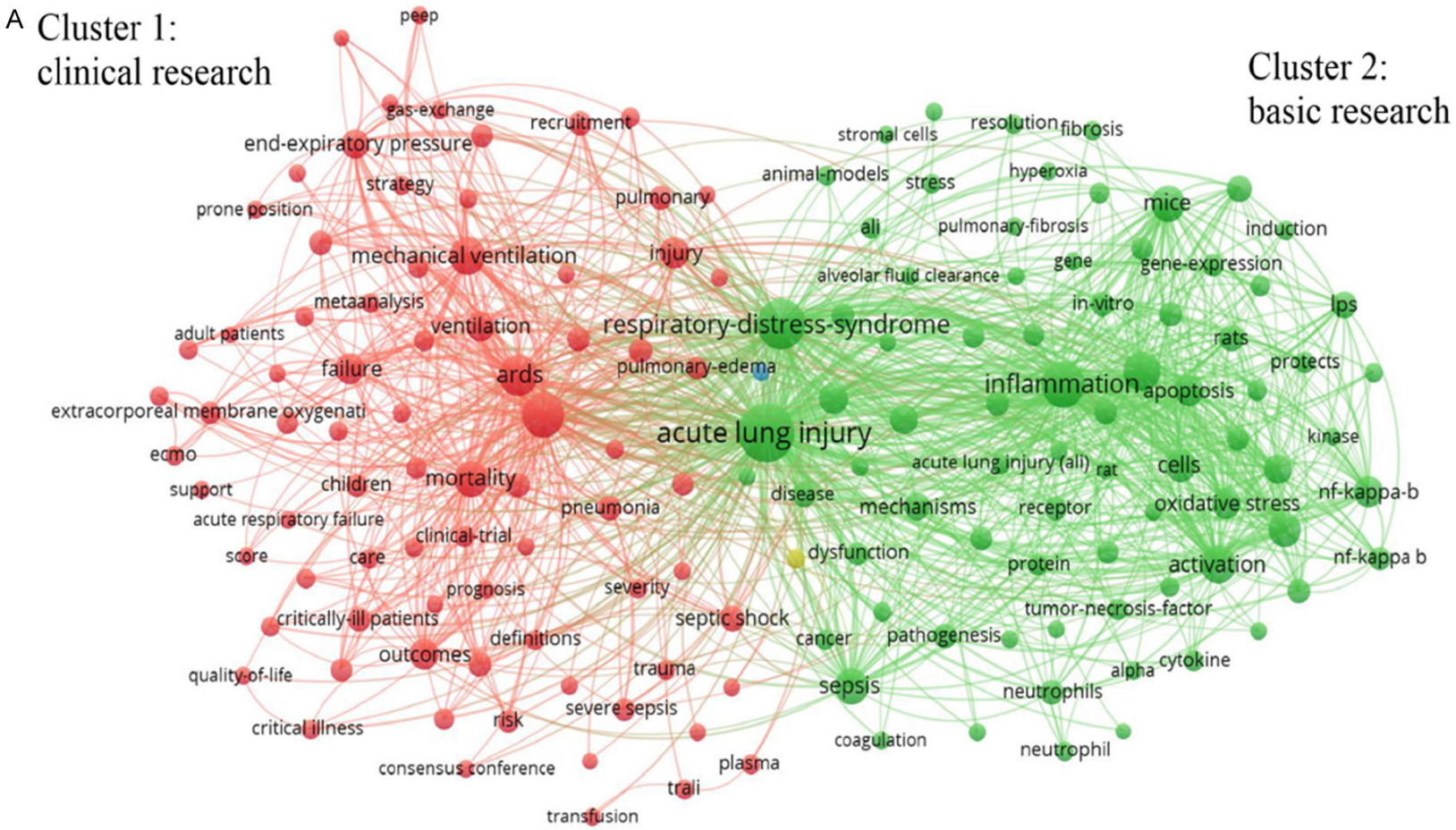
Title	Corresponding authors	Journal	Publication Year	Total Citations
Acute Respiratory Distress Syndrome The Berlin Definition	Rubenfeld, GD	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2012	2938
Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome.	Papazian, L	NEW ENGLAND JOURNAL OF MEDICINE	2010	1091
Functional Disability 5 Years after Acute Respiratory Distress Syndrome	Herridge, MS	NEW ENGLAND JOURNAL OF MEDICINE	2011	1050
Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico	Perez-Padilla, R	NEW ENGLAND JOURNAL OF MEDICINE	2009	1047
Prone Positioning in Severe Acute Respiratory Distress Syndrome	Guerin, C	NEW ENGLAND JOURNAL OF MEDICINE	2013	1002
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries	Laffey, JG	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2016	983
Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome	Davies, A	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2009	908
H1N1 2009 influenza virus infection during pregnancy in the USA	Jamieson, DJ	LANCET	2009	872
Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome Systematic Review and Meta-analysis	Meade, M	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2010	716
Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A (H1N1) Infection in California	Louie, JK	AMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2009	710

Definition on Jama-Journal of the American Medical Association (IF 51.27) by Rubenfeld GD ranked the first with 2938 citations, followed by Papazian L and Herridge MS, with 1091 and 1050 citations respectively. Details are showed in **Table 2**.

Analysis of keywords in ALI/ARDS

We analyzed all included 7,890 articles using the VOSviewer. In **Figure 5A**, 159 keywords (defined as terms that occurred more than 75 times appeared in titles and abstracts in all publications) were divided into 2 groups: “clinical research” (left, in red) and “basic research” (right, in green). In clinical research, the keywords with the highest frequency are: acute respiratory distress syndrome (1387 times), ARDS (1166 times), mechanical ventilation (870 times), mortality (799 times) and injuries (517 times). In the basic research, the words are: acute lung injuries (3696 times), respiratory-distress-syndrome (2301 times), inflammation (1555 times), expression (1043 times) and activation (909 times). Detailed showed in Supplementary Table 1.

The distribution of keywords in different time periods were indicated (**Figure 5B**). Chronological order is presented from dark blue to bright yellow. In cluster 2, the earliest keywords


A
Cluster 1:
clinical research
Cluster 2:
basic research
peep
gas-exchange
recruitment
end-expiratory pressure
strategy
prone position
pulmonary
mechanical ventilation
injury
metaanalysis
ventilation
adult patients
failure
ards
pulmonary-edema
extracorporeal membrane oxygenati
ecmo
support
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acute respiratory failure
clinical-trial
score
care
prognosis
severity
critically-ill patients
septic shock
definitions
outcomes
quality-of-life
trauma
severe sepsis
risk
critical illness
consensus conference
plasma
trali
transfusion
respiratory-distress-syndrome
acute lung injury
pneumonia
disease
dysfunction
mechanisms
receptor
protein
cancer
pathogenesis
sepsis
coagulation
neutrophil
neutrophils
alpha
cytokine
tumor-necrosis-factor
activation
oxidative stress
nf-kappa-b
nf-kappa b
kinase
cells
acute lung injury (ali)
rat
inflammation
apoptosis
protects
rats
lps
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stress
animal-models
stromal cells
resolution
fibrosis

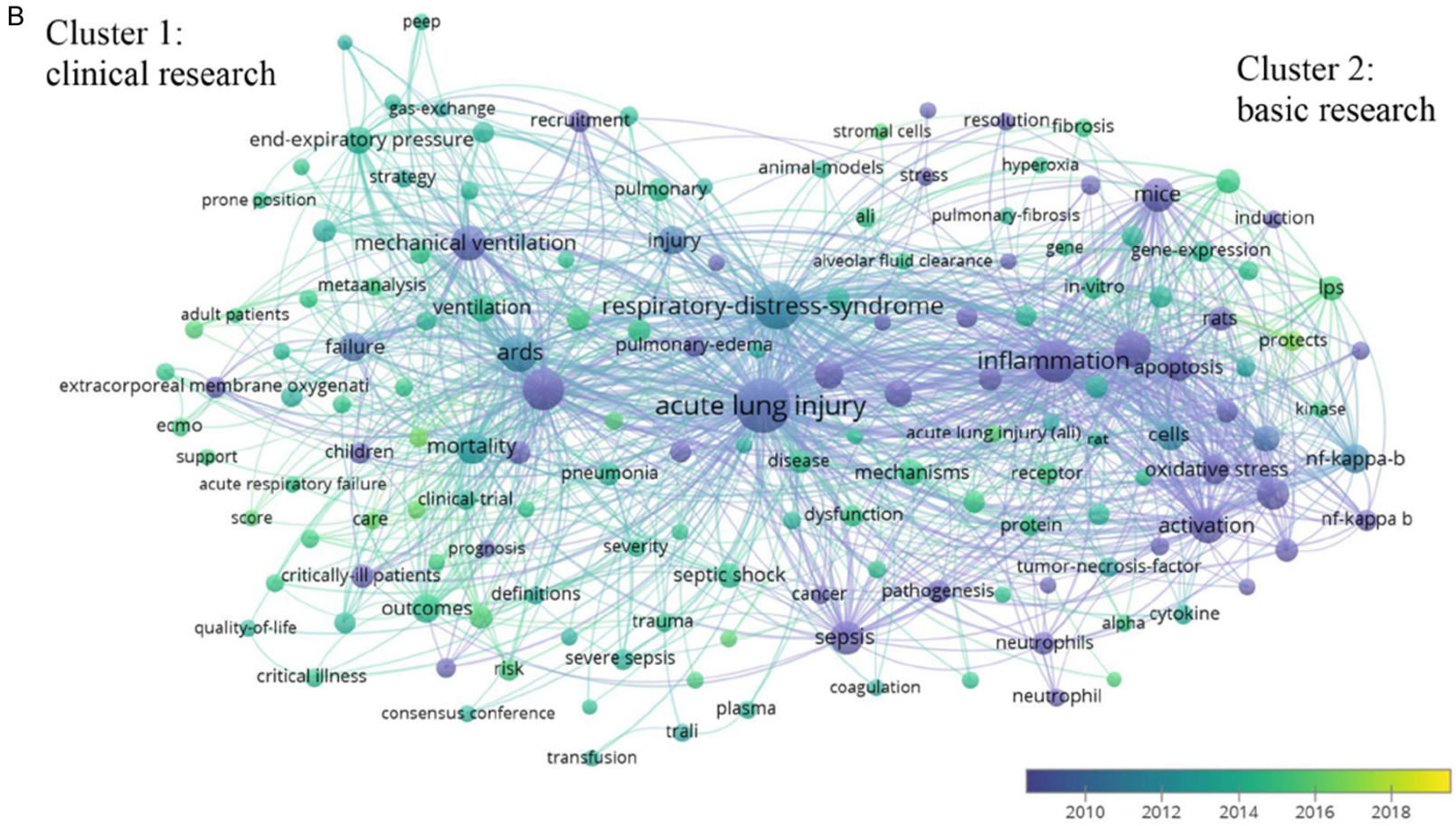

Figure 5. The mapping of keywords in ALI/ARDS studies.

were “expression” (cluster 2, AAY 2009.0) with 1043 times, the latest words were “protects” (cluster 2, AAY 2016.5) with 155 times. In cluster 1, the earliest words were “mechanical ventilation” (cluster 1, AAY 2009.4) 870 times, and the latest word was “Berlin definition” (cluster 1, AAY 2016.3) with 161 times. Referring to the color intensity, we found that the research hotspot on ALI gradually shifted from the basic research to clinical treatment in recent years (**Figure 5B**).

Discussion

In the present study, we reviewed 7890 papers on ALI/ARDS, and found the number of global publications per year increased gradually and rapidly (**Figure 3**). The major finding was that the USA was the most productive and published most highly cited studies, resulting a much higher H-index than other countries (H-index: 107) (**Figure 2A**). Besides, in the top 10 authors with most publications in research scope of acute lung injury, 4 were American researchers (**Table 1**) and 11 in 20 in the top 20 institutions were from USA (**Figure 4B**). However, China was noteworthy of the rapid growth, and the publication number has surpassed the USA since 2016 (**Figure 2B**). For journals, Critical Care Medicine was the most popular journal and published 295 articles, which accounts for 3.74% (**Figure 4A**). The top 10 high-cited papers related to ALI/ARDS, all published in the most famous clinical journals (New England Journal of Medicine, JAMA, and Lancet) (**Table 2**). What’s more, keywords extracted from the titles and abstracts were stratified into two major clusters “Basic Research” and “Clinical Research” (**Figure 5A**) by VOSviewer software and a research trend indicated that basic research was gradually transforming into clinical research (**Figure 5B**). Furthermore, “berlin definition”, “stromal cells” and “protects” might be the latest potential ‘hotspots’ in the research of the ALI/ARDS (Supplementary Table 1).

Since ARDS was originally defined in 1967 with a case report in critically ill patients, considerable researches have been made to explore the pathogenesis and pathophysiology of the ALI [7, 22, 23]. In the past decade, the number of publications every year in the field of ALI/ARDS increased stably due to its high mortality at 30-40% [24]. However, as for the trend of RRI in ten years, the curve shows a downward trend in volatility overall (**Figure 2B**). Nowadays, the management of ARDS patients mainly focuses on a lung-protective ventilation strategy and no specific pharmacotherapies have been formulated [24], which may weaken the researchers’ interest, confidence and persistence on the disease to some extent. In support, it is evident shown in the RRI curve that there was a sharp increase in 2012 (**Figure 4A**). During that time, the Berlin definition [25] was a milestone for the identification and diagnosis of ARDS and contributed the progress of related research, which is consistent with high-cited papers entitled “Acute Respiratory Distress Syndrome: The Berlin Definition”. It is the top 1 high-cited papers related to ALI with the total citations of 2938, much more than other articles (**Table 2**). The research results suggest that the proposal of guidelines or definitions will help promote the progress and development of research in this field. Therefore, regarding ALI/ARDS research, we should continue to enrich its definitions and guidelines.

As to the country contribution, the USA was the most productive region and has made the greatest contribution in researches on ALI/ARDS, evidenced by the number of publications, H-index, and citation frequency. Moreover, in the top 10 authors with most publications (**Table 1**), four of them were American, which may promote the ALI/ARDS research advancement in America, the same publication trend can also be documented in other diseases and related research, such as osteoporosis [26], diabetes [27], pancreatic diseases [28], etc. Given the fact that the diagnostic criteria of ARDS was initially defined by American and European scholars on the American-European Consensus Conference (AECC) in 1994 [29], when the diagnosis of ARDS were made scientific. The USA focused on this disease or issue earlier than the rest of the world, this also explains why it is by far the most publicized country. Although Chinese scholars did not participate in the proposal of standards and started late in the studying the disease, the number of publications ranked second and two Chinese scholars were among the top 10 authors with most publications (**Table 1**). Large population base determines higher number of ARDS-related patients, for example, a cross-

sectional study in 20 participating Chinese ICUs enrolled 1,814 patients found 149 (8.2%) and 147 (8.1%) patients were diagnosed of ARDS by AECC and Berlin definition, respectively [30]. A study retrospectively analyzed 925 preterm infants with respiratory distress in China mainland and the number of ARDS infants was 49, which accounted for 5.29% [31]. Therefore, gradually accumulated relevant diagnosis or treatment experience have promoted the research of the disease, explaining why the annual publications related to ALI/ARDS in China sustained a rapid growth and has exceeded the USA since 2016 (**Figure 3**). However, we cannot deny the fact that China has not achieved high citation frequency or high H-index as the USA (**Figure 2A**). The imbalance between the quantity and quality of publications in China might attribute to several reasons. Firstly, the number of publications in China mainland was much less than that in the USA and German in 2009, under the global trend (**Figures 2** and **3**), and it is evident the Chinese research on the ALI/ARDS started relatively later. Secondly, ARDS is a disease diagnosed from clinical symptoms based on clinical evidences. China reports relatively more on observational studies with lack of high-quality multicenter Randomized Clinical Trials (RCTs), leading to insufficient solid evidences in clinical practices. Thirdly, there are many other studies in China on the therapeutic effect of traditional Chinese medicine in ALI/ARDS. For instance, Yam glycoprotein, separated from traditional Chinese yam, has anti-inflammatory and immunomodulatory effects on the lipopolysaccharide (LPS)-induced ALI mice [32]. A study enrolled 53 patients in ICU with ARDS to observe the effects of Xuanbai Chengqi decoction on lung compliance [33]. There is no doubt that the utilization of traditional Chinese medicine provides new options for clinical treatment of ALI/ARDS, but traditional Chinese medicine is difficult to be verified by modern medicine, due to its multi-component, multi-target and mostly unknown mechanisms. ALI/ARDS is common cause of respiratory failure and associated with several clinical disorders including sepsis, trauma, pneumonia, and aspiration. Therefore, the study of the disease requires multidisciplinary communication and cooperation, which are not limited to a certain country/region or individual researchers.

Among the top 20 institutions, The USA owned 11 institutions from the top 20 institutions in researches with regard to ALI/ARDS, followed by Canada, China, France and Brazil, indicating its dominant role in this field (**Figure 4B**). University of California San Francisco that had published the most articles in such area belonged to USA. and two authors (MATTHAY MA and CALFEE CS) who were top 10 authors with most publications are from the same university (**Table 1**). The United States possesses the most elite institutions around the world, which in turn supports its leading position. Besides, there were 6 institutions in China and 2 in Canada as well, and the rank was roughly consistent with publications numbers that from the USA (rank 1), China (rank 2), Canada (rank 4) (**Figure 2A**). Regions and institutes play a vigorous ongoing role for further publications [34], thus, more elite institutions are to be built to improve the international status in the significant directions associated with ALI/ARDS, and still, partnerships among top institutes/regions could be a good choice.

Of note, the journal of Critical Care Medicine had published 295 papers in the field, ranking the first. Critical Care Medicine mainly publishes clinical and basic research in critical illness, and ARDS as a respiratory failure is common in critical ill patients, which is in line with the journal aims and scopes. According to a cross-sectional research of 29,144 patients from 50 countries [35], the prevalence of ARDS in ICU patients was 10%, and ARDS was identified in 23% of all ventilated patients. The same reason is applied for the journal of Critical Care (rank 4). PLOS One ranks second and is a comprehensive journal, which is well known for its big publication numbers, for example, it has published 19,150 papers in 2018 according to WOS. American Journal of Physiology Lung Cellular and Molecular Physiology (rank 3) and International Immunopharmacology (rank 5) mainly focused on basic research. Mature animal models such as LPS, pulmonary ischemia, oleic acid-induced model have been developed for basic research in ALI [36]. Meanwhile, the number of publications ranking at the fifth drops from 168 to 140 as of at the tenth (**Figure 2A**), and it suggests that future focus is more likely to be published in the aforementioned journals.

High-cited papers lead to tremendous academic impact. The detailed information about the top 10 cited publications within ALI/ARDS are listed in **Table 2**. The paper entitled "Acute Respiratory Distress Syndrome: The Berlin Definition" had been cited for 2938 times, which was the most cited papers. This study is published on JAMA in 2012 and introduced the evolution from "AECC Definition" to "The Berlin Definition" in detail. Compared with the AECC definition, this Berlin Definition combined consensus discussions with empirical evaluation to form evidence-based, critical illness syndrome definitions accurately, with better predictive validity for mortality [25]. A clinical study that rank second entitled "Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome" is published in the New England Journal of Medicine. This study was a multicenter, double-blind trial that included 340 patients with an onset of severe ARDS to explore the role of neuromuscular blocking agent on 90-day survival rate [37]. All the top 10 high-cited articles were about clinical researches and were published at the top 4 most influential clinical journals (**Table 2**), highlighting the essence of the ARDS: a clinical presentation in critically ill patients [24].

To explore the research tendency and latest hotspot, visualized mapping portrayed by VOSviewer was applied. In the past decades, keywords were divided into 2 groups: "clinical research" and "basic research" (**Figure 5**). In the basic research, the pathophysiology of ALI/ARDS, and the mechanisms of injury were explored. There were two main directions [7]: dysregulated inflammation following the activated innate immune response by DAMPs (Danger-Associated Molecular Patterns) [38] and alveolar barrier disruption that increased permeability of microvascular barriers or low rate of alveolar fluid clearance, resulting in accumulation of protein-rich edema fluid [39]. The fundamental mechanisms of ALI/ARDS remain elusive, despite of more than 50 years of research [40]. Therefore, this study suggests that in view of the complex pathophysiological mechanism of ALI/ARDS, researchers should start from the mechanism and establish a unified cell and animal model. Clinically, the content of research covers various aspects including definition, diagnosis, histopathology, pathophysiology, therapeutic methods, etc [1]. Especially, treatment has been optimized for the refinements in ventilator and fluid management [41], supported by evidence from prospective randomized trials. Interestingly, a gradual shift in terms of focus from the "basic research" to the "clinical research" appeared in the time-period map (**Figure 5B**). Although several models of experimental ALI/ARDS have been developed, none have fully captured the etiologies, initial inflammation, heterogeneity of human ARDS [40]. Instead, more and more high quality clinical researches have provided insights and understanding. However, the importance of basic research is not to be ignored. ARDS is a syndrome with a broad clinical phenotype including mild, moderate and severe, and it has been challenging to translate the results of animal and cell studies to pharmacologic therapies [7], This is also a key issue restricting the progress of basic research. For example, potentially targetable inflammatory mediators, beneficial in basic research, could not be applied on the clinical ill patients. In the future, optimized design of ALI/ARDS studies is essential for ongoing interaction among basic scientists, clinicians and translational scientists.

The keyword "protects" appeared most recently with an AAY of 2016.5 (Supplementary Table 1). Nowadays, effective treatments for patients with ARDS are mainly lung protection strategies, such as the optimization of small tidal volume ventilation. An ongoing RCT (Randomized Controlled Trial) will test the possibility of improving survival by further lowering tidal volume to 4 ml/kg and plateau pressures to 25 cmH_2O. Besides, important signaling pathways or molecules were discovered in basic researches continuously such as that miR-424 overexpression protects alveolar epithelial cells from LPS-induced ALI via the NF-κB pathway. Especially, cell-based therapy has emerged promising for the treatment of ALI/ARDS, which is also confirmed in our study with the third newest keyword "stromal cells". Bone marrow-derived stromal cells have been shown to enhance recovery from lung injury, and increasing ATP concentration in alveoli and mesenchymal stromal cells (MSCs) have demonstrated putative effects on experimental ARDS. Therefore, the results of this study prompts that the direction of follow-up research may mainly focus on the protection of organs, maintaining and protecting lung function through cell thera-

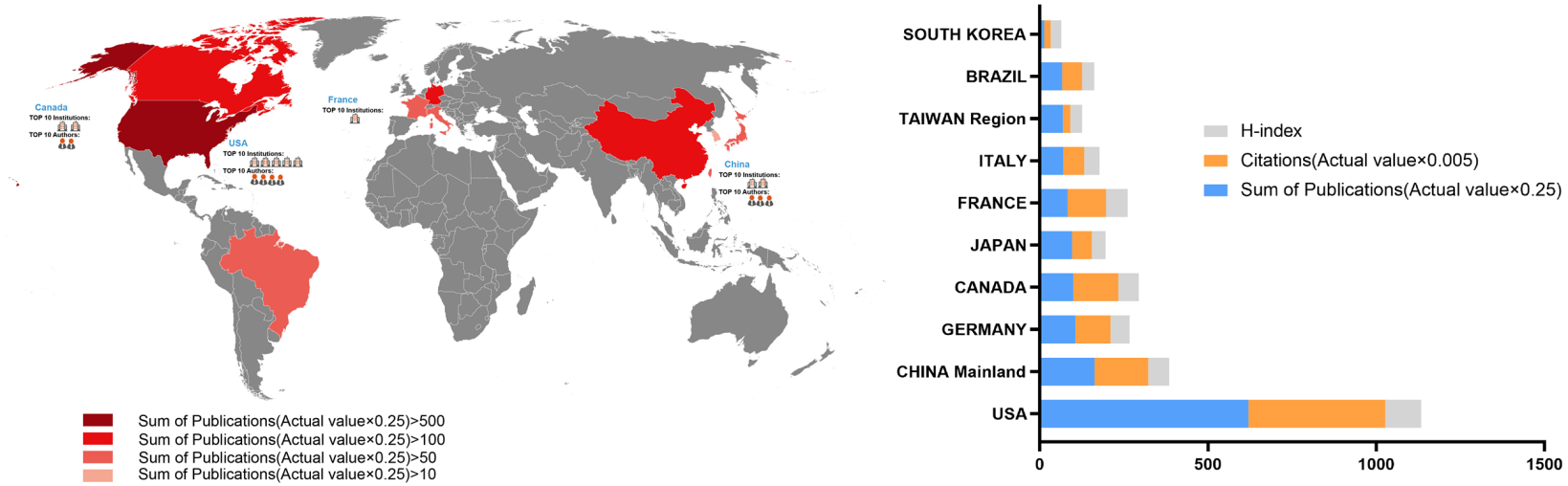

Figure 6. Publication trends of research on ALI and ARDS.

py and mechanical ventilation etc. In "clinical research" cluster, "Berlin definition" is the newest word (Supplementary Table 1). The definition of the ARDS has always been controversial. A study has compared the prevalence and outcomes of pediatric ARDS using PALICC (Pediatric Acute Lung Injury Consensus Conference Criteria) and Berlin definition, suggesting the PALICC criteria identified more number of patients with ARDS. In the future, breakthroughs may be succeeded upon the aforementioned hotspots.

This bibliometric analysis investigated the publications that were extracted from the Web of Science database of Science Citation Index Expanded journals. The data analysis is fairly comprehensive and objective. However, limitations are inevitable. Due to our inclusion criteria, we enrolled publications only in English in the present investigation which may exclude some important non-English studies related to ALI/ARDS. In addition, papers published in 2019 were not all incorporated, which means the analysis did not contain any keywords from 2019. The last but not the least, the database is still open for updating studies continuously, so a slight discrepancy between bibliometric analysis results and actual research situation may exist.

Conclusions

Taken together, the present study has summarized and analyzed the global research trends concerning ALI/ARDS. The USA has made the biggest contribution in regards of number and impact of publications. Although China has produced a considerable quantity of publications with very rapid growth, the quality of these papers are expected to be increase correspondingly (**Figure 6**). For journals, though Critical Care Medicine was the most popular journal and latest studies, novel progresses were also published in the top 4 clinical medicine journals. In two main clusters, "Basic Research" and "Clinical Research", several keywords such as "berlin definition", "stromal cells" and "protects" appear to be the latest potential hotspots in the field of the ALI/ARDS, suggesting possible trends of research focus.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. The analytic consequence of 159 keywords with at least 75 occurrence times

No.	Label	Cluster	Links	Occurrences	Average appearing years (AAY)	Average citations
1	activation	2	145	909	2004.2211	14.9021
2	acute kidney injury	1	112	81	2015.2469	18.1975
3	acute lung injury	2	158	3696	2009.6794	20.1426
4	acute lung injury (ali)	2	112	110	2015.6909	11.3364
5	acute respiratory distress syndrome	1	156	1387	2004.504	16.4037
6	acute respiratory distress syndrome (ards)	1	129	105	2015.4857	10.181
7	acute respiratory failure	1	89	77	2014.5974	26.1558
8	acute respiratory-distress	1	129	100	1974.4	17.35
9	adult	1	108	113	2014.6195	23.2566
10	adult patients	1	87	75	2014.8667	20.1867
11	adults	1	103	115	2014.7217	19.7739
12	ali	2	135	144	2014.8333	14.5417
13	alpha	2	103	93	2014.8387	18.2366
14	alveolar fluid clearance	2	95	87	2014.7126	24.5172
15	alveolar macrophages	2	100	131	2014.3359	19.0076
16	alveolar recruitment	1	61	76	2013.1842	16.9474
17	animal-models	2	119	112	2013.9911	14.9554
18	apoptosis	2	128	465	2006.5462	13.686
19	ards	1	158	1166	2011.2316	17.6535
20	berlin definition	1	114	161	2016.2609	22.9255
21	biomarkers	1	106	78	2015.7308	16.2564
22	bronchoalveolar lavage	3	102	77	2013.5195	12.6753
23	cancer	2	113	121	1998.4793	13.2562
24	care	1	115	129	2016.0388	14.3023
25	cells	2	131	563	2011.4245	14.8082
26	children	1	117	188	2003.7234	19.6117
27	clinical-trial	1	128	163	2013.7423	51.4724
28	coagulation	2	104	91	2013.2857	20.8791
29	consensus conference	1	89	78	2013.5641	26.2692
30	corticosteroids	1	114	98	2014.1735	15.2857
31	critical illness	1	93	106	2014.1981	36.0283
32	critically-ill	1	108	83	2013.3253	31.1928
33	critically-ill patients	1	124	245	2005.498	51.2571
34	cytokine	2	113	132	2013.303	19.7955
35	cytokines	2	141	252	2006.1905	14.5437
36	damage	2	95	76	2015.4342	12.5132
37	death	2	111	78	2014.3718	22.8077
38	definition	1	106	115	2015.9565	18.1043
39	definitions	1	123	124	2013.0887	31.6855
40	diagnosis	1	87	84	2014.7143	26.5714
41	disease	2	149	247	2014.5304	22.0729
42	distress-syndrome	1	122	170	2013.3706	25.1118
43	dysfunction	2	144	202	2014.901	19.005
44	ecmo	1	84	125	2015.16	10.632
45	end-expiratory pressure	1	132	437	2013.8673	26.0046
46	endothelial-cells	2	114	184	2013.8641	20.5326

47	endotoxin	2	123	228	2013.6184	17.7193
48	epidemiology	1	145	209	2015.488	35.9569
49	epithelial-cells	2	113	177	2013.8927	18.904
50	expression	2	147	1043	2009.0451	14.6577
51	extracorporeal membrane oxygenation	1	99	185	1993.2432	16.1297
52	extracorporeal membrane-oxygenation	1	90	113	2015.5044	15.5398
53	factor-kappa-b	2	90	80	1988.575	16.9375
54	failure	1	144	465	2010.0495	23.8086
55	fibrosis	2	105	128	2014.8828	13.3438
56	gas-exchange	1	97	97	2012.9897	15.8247
57	gene	2	97	81	2014.2222	15.3704
58	gene-expression	2	108	183	2013.9727	20.6557
59	hyperoxia	2	96	94	2014.2021	18.5851
60	identification	2	113	101	2014.5644	22.2673
61	impact	1	101	79	2015.1013	27.6076
62	in-vitro	2	126	237	2014.4515	18.8312
63	in-vivo	2	123	251	2013.5578	25.4502
64	induction	2	101	130	1999.2769	15.0308
65	infection	1	133	177	2002.8927	51.7006
66	inflammation	2	155	1555	2007.3158	14.9659
67	inflammatory response	2	132	186	2014.9892	12.8387
68	inflammatory responses	2	97	77	1988.1039	34.013
69	inhibition	2	128	413	2010.1792	13.6634
70	injury	1	156	517	2010.3346	19.1857
71	intensive-care	1	94	117	2014.9573	19.1624
72	intensive-care-unit	1	105	168	2013.7381	69.631
73	ischemia-reperfusion	2	97	80	2014.325	12.0125
74	ischemia-reperfusion injury	2	102	119	1996.7563	16.8067
75	kappa-b	2	89	128	1999.1875	14.8594
76	kinase	2	94	90	2014.9444	17.9111
77	life-support	1	81	102	2014.6667	36.5392
78	lipopolysaccharide	2	138	642	1999.1059	15.4611
79	lps	2	109	258	2015.376	14.1047
80	lung	2	146	213	2013.5493	16.6901
81	lung injury	2	156	504	2006.8591	12.9901
82	macrophages	2	122	304	2014.9671	19.7434
83	management	1	133	207	1995.3237	13.9179
84	mechanical ventilation	1	158	870	2009.4103	24.8874
85	mechanism	2	104	87	1992.4023	13.8391
86	mechanisms	2	149	366	2014.623	15.2186
87	metaanalysis	1	110	116	2014.9828	24.6983
88	mice	2	142	731	2006.6867	16.2654
89	model	2	152	434	2005.2811	13.371
90	mortality	1	158	799	2012.567	23.7359
91	multicenter	1	100	105	2015.0762	26.3048
92	necrosis-factor-alpha	2	97	79	2013.0759	19.5316
93	neutrophil	2	111	116	1996.9138	16.3879
94	neutrophils	2	126	248	1998.0847	17.0565
95	nf-kappa b	2	101	197	1995.4315	13.0914

96	nf-kappa-b	2	120	492	2011.1951	14.6911
97	nitric-oxide	2	125	184	2013.8533	14.7609
98	nitric-oxide synthase	2	105	149	2013.0268	18.4966
99	outcomes	1	146	503	2014.4751	33.4732
100	oxidative stress	2	136	518	2003.5772	12.9595
101	oxygenation	1	118	116	2013.9741	14.3707
102	pathogenesis	2	141	254	2006.7559	17.0748
103	pathophysiology	2	107	82	2014.4512	12.9268
104	pathway	2	113	232	2007.0431	11.7284
105	peep	1	66	78	2014.0385	13.1154
106	permeability	2	124	195	2003.7641	18.3128
107	plasma	1	107	123	2013.8049	25.9268
108	pneumonia	1	146	243	2013.893	17.8724
109	pressure	1	120	160	2014.6	38.1313
110	prevention	1	126	86	2014.5465	17.4651
111	prognosis	1	104	80	1964.45	27.325
112	prone position	1	78	80	2014.3875	12.6125
113	protects	2	101	155	2016.4645	9.329
114	protein	2	116	147	2014.7007	18.6259
115	pulmonary	1	148	213	2014.2676	17.7606
116	pulmonary edema	2	116	96	2013.2917	28.0938
117	pulmonary-edema	1	143	168	2001.1964	24.2738
118	pulmonary-fibrosis	2	95	90	2013.7556	21.8556
119	quality-of-life	1	72	81	2013.7037	45.9136
120	randomized controlled-trial	1	123	221	2013.276	39.5882
121	rat	2	100	98	2013.5204	11.9184
122	rats	2	125	290	2007.4276	13.5724
123	receptor	2	133	202	2015.0396	18.3218
124	recruitment	1	140	243	2005.9753	25.9218
125	release	2	105	80	2014.3	14.975
126	repair	2	92	80	1988.6875	26.0875
127	resolution	2	104	128	1999.9844	16.7656
128	respiratory distress syndrome	1	122	116	2014.6466	18.3793
129	respiratory failure	1	94	98	2013.9286	12.3673
130	respiratory-distress-syndrome	2	156	2301	2011.3585	22.2634
131	responses	2	109	133	1999.5789	14.9925
132	risk	1	117	179	2015.2011	16.2737
133	risk-factors	1	116	155	1988.6065	20.2774
134	score	1	84	77	2015.5584	18.0909
135	sepsis	2	153	749	2004.0801	22.6756
136	septic shock	1	145	270	2014.2222	37.037
137	severe sepsis	1	135	173	2013.5549	57.8497
138	severity	1	118	103	2014.165	25.9903
139	shock	4	134	113	2013.6283	15.7965
140	strategy	1	100	125	2013.024	39.848
141	stress	2	116	106	1995.6132	13.8396
142	stromal cells	2	86	87	2015.4828	29.8966
143	support	1	75	78	2015.0769	17.8205
144	surfactant	1	123	100	2013.27	15.92

145	survival	1	151	232	2015.056	23.7198
146	therapy	1	145	238	2014.7185	21.979
147	tidal volume	1	119	168	2013.5893	22.4405
148	tidal volumes	1	99	93	2013.7097	20.7312
149	tnf-alpha	2	118	203	2004.6355	15.0493
150	trali	1	68	115	2012.9652	20.3043
151	transfusion	1	89	88	2013.5341	17.6591
152	transplantation	2	113	95	1992.6	16.7158
153	trauma	1	117	101	2014.5248	13.198
154	trial	1	115	154	2013.8182	18.7857
155	tumor-necrosis-factor	2	108	146	2012.8014	19.2671
156	united-states	1	98	75	2014.16	30.16
157	ventilation	1	152	427	2014.363	19.918
158	ventilator-induced lung injury	1	127	124	2014.0242	23.1935
159	volume	1	80	89	2014.5843	16.6742