

Bibliometric Analysis of Literature on Acute Respiratory Distress Syndrome Treatments Published Between 2000 and 2019

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a common and extensively researched condition, and treatment modalities are continuously being developed and improved. Although the literature on ARDS treatment is vast, only one prior bibliographic analysis of trends in this area has been published. Objective We aimed to systematically evaluate the literature on ARDS treatments published between 2000 and 2019 from the perspective of bibliometrics. Research design and methods: Literature retrieval was performed in PubMed and in Web of Science Core Collection. Studies were analyzed by publication and temporal trends. CiteSpace was used to perform Co-occurrence analysis for institutions and reference co-citation analysis for research topics. Burst keyword detection was used to predict future areas of research interest in the field. Findings: A total of 13,933 articles were retrieved. The journal *Critical Care Medicine* published the largest number of articles (956, 6.86%). The University of Toronto was affiliated with the most publications (574, 4.28%) and had the highest degree of betweenness centrality, indicating extensive inter-institution collaboration. The papers on ARDS treatment published between 2000 and 2019 were grouped into 10 major clusters, three of which indicated recent activity ("acute lung injury," "long-term outcome," and "extracorporeal membrane oxygenation"). Fifteen burst keywords/terms were identified, including extracorporeal membrane oxygenation, meta-analysis, and oxidative stress. Implications: On the basis of the literature published in the preceding 20 years, the study of ARDS treatment is an ongoing concern. Extracorporeal membrane oxygenation was an active focus of research in this field. It and oxidative stress are likely to become major topics of research interest in the near future. Meta-analysis will be a popular method in analyzing the efficacy of ARDS treatments.

Keywords: Acute respiratory distress syndrome, Treatment, Visualization analysis, Bibliometrics, Reference co-citation analysis.

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Received: 13-06-2022;

Revised: 21-11-2022;

Accepted: 16-02-2023.

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a clinical syndrome characterized by non-cardiogenic pulmonary edema, diffuse endothelial injury, and bilateral pulmonary infiltrates, which can be devastating to critically ill patients in the intensive care unit and places a burden on the healthcare system. The LUNG SAFE study reported that 23.4% of patients receiving mechanical ventilation were ARDS cases and that the hospital mortality rate in patients with severe ARDS was 46.1%.^[1] The first report of the syndrome was published in 1967,^[2] and discussions of how best to define the new clinical entity have been ongoing,

from the American-European Consensus Conference definition to the Berlin definition, and the same is true for developments in ARDS treatment. In 1969, a treatment with continuous positive-pressure breathing was proposed,^[3] and Positive End-expiratory Pressure (PEEP) therapy was evaluated in 11 ARDS patients in 1973.^[4] Ventilation with a low tidal volume (6 mL/kg predicted body weight) and a plateau pressure of 30 cm of water or less was shown to improve survival in patients with ARDS,^[5] and these strategies are recommended in clinical practice guidelines. ARDS management strategies are more developed than therapies. Recruitment maneuvers, the technique that sustains high airway pressure for a period of time so as to expand the collapsed alveoli during mechanical ventilation, are still under debate, although they can reverse hypoxemia.^[6] The findings of a recent randomized clinical trial did not support the routine use of recruitment maneuvers and titrated PEEP because of increased 28-day mortality in patients with moderate to severe



DOI: 10.5530/jscires.12.2.038

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ARDS.^[7] These examples illustrate the evolution in thinking and clinical practice around the treatment of ARDS, but individual examples cannot provide a comprehensive overview of this evolution. The entire published literature on ARDS, however, contains a detailed history of this evolution in terms of trends, leading journals in the publication of ARDS research, and the investigators and institutions behind this research, along with their interrelationships and influences.

A detailed and comprehensive overview of this nature may provide policy makers and funding agencies with important information to facilitate identification of key research topics, current trends, or priority areas for funding in this field. Although ARDS treatments have been reviewed,^[8,9] only one bibliometric analysis has examined the trends in topics, authors, and research institutions. Wang and colleagues analyzed trends in ARDS research, compared publication years, institutions, journals, and highly cited articles, and divided the articles into clinical and basic research clusters by keywords,^[10] an approach that is not sufficiently detailed and comprehensive. Recognizing the absence of such a published survey, we undertook to perform a bibliographic analysis of papers related to ARDS therapy published over the past 20 years. Bibliometric analysis is a useful method for identifying impactful authors and regions, constructing collaboration networks, and distilling key research topics in particular areas.^[11]

Objectives and Scope of the study

In this study, bibliometric analysis was used to achieve three goals: (1) map the overall layout of ARDS research from the perspective of publication dates, journals, keywords, and citations, (2) identify core research institutions and their direct collaborative networks, and (3) highlight current and potential future areas of research focus.

METHODOLOGY

Data collection

Literature retrieval was performed in both PubMed and Web of Science Core Collection on August 3, 2020. We selected “respiratory distress syndrome, adult” as a subject heading, which was combined in PubMed searches with several subheadings (therapy, diet therapy, drug therapy, nursing, prevention and control, and surgery). We then searched for ARDS treatment-related articles in Web of Science using the same strategy. Both sets of records were merged and duplicates were removed. Articles, reviews, and letters published between 2000 and 2019 (inclusive) were kept for further analysis. Figure 1 shows a flowchart of the literature retrieval strategy. Online Supplement 1 provides more details on the retrieval process. Informed consent was not necessary as our study analyzed published literature without any identifying information about participants in the research reported.

Analysis and visualization

The articles identified in the search were systematically analyzed using the Web of Science website and CiteSpace (5.7.R1, Chaomei Chen).^[12] Web of Science has built-in statistics tools to graph publication trends by year, language, and journal. CiteSpace is a tool for visualizing and analyzing scientific literature by constructing the knowledge architecture by citation relationship between studies in the research field. Among the bibliometric analysis methods, we selected reference co-citation analysis^[13] and analysis of institutional collaboration networks for articles published between 2000 and 2019.^[14] The indicators used in the evaluation were “modularity” and “betweenness centrality,” as follows. The degree to which a network can be divided into several independent blocks is measured by modularity.^[15] Its value ranges from 0 to 1, and a relatively high value means a well-structured network.^[16] Betweenness centrality is a quantitative indicator of the influence of institutions, calculated as the fraction of shortest paths going through a given node that denotes an institution in the cooperative network.^[17] A citation is regarded as a reasoned and solid index of scientific communication. Co-citation analysis enables the identification of the inner structure of research disciplines. A co-citation exists if two references or authors appear in the same bibliography, and is interpreted as the measure for similarity of content of the two references or authors.^[18] In this study, the 50 most-cited articles in successive 3-year intervals (e.g., 2000–2002, 2003–2005) were collected, and all references from each 50-article block were used to create the individual networks. Log-likelihood ratio weighting was used to analyze the contents of each cluster. “Burst keyword detection,” a computing technique used to identify mutations in information, was used

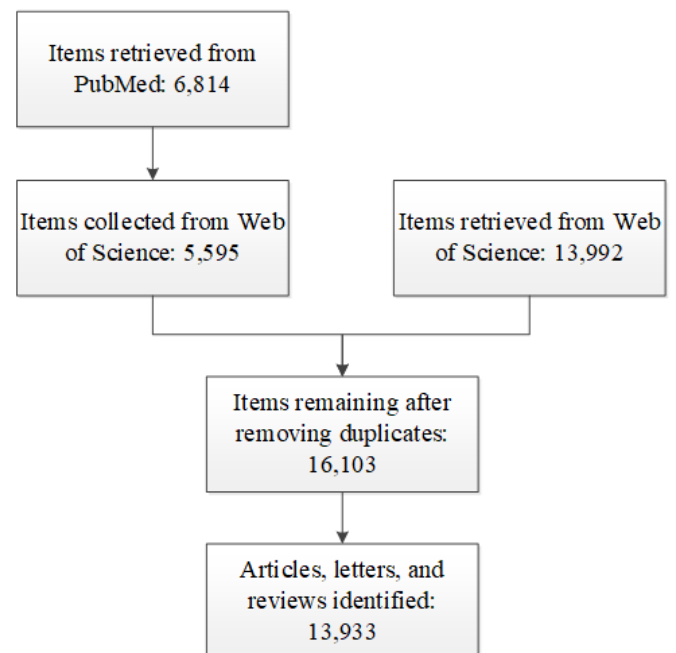


Figure 1: Flowchart of literature selection.

to determine new research foci in the field.^[19] A keyword burst is characterized by the intensity of the burst and by its duration.

RESULTS

Temporal distribution of papers

A total of 13,933 papers were collected for analysis. Figure 2 graphs the number of articles published by year and indicates a general upward trend in research into ARDS treatments, from 466 articles in 2000 to 918 in 2019.

Publication language

The articles returned in the search had been published in 15 languages. Of the 13,933 papers, 13,460 (96.61%) were published in English, 221 (1.59%) in German, 121 (0.87%) in French, 89 (0.64%) in Spanish, 15 (0.11%) in Portuguese, and 27 (0.2%) in other languages.

Core journals

A total of 1,592 scholarly journals published articles on ARDS treatment during the period of interest. The 10 journals that published the most articles (Table 1) accounted for 28.1% of all documents published (3,914 articles). The journals publishing the most ARDS research were *Critical Care Medicine*, *Intensive Care Medicine*, *American Journal of Respiratory and Critical Care Medicine*, and *Critical Care*.

Research institutions

The researchers who published the literature included in this study were affiliated with a total of 9,468 institutions. Table 2 lists the

15 institutions most associated with publishing ARDS treatment research, which accounted for 28.64% of the total articles. The University of Toronto was associated with the most publications, followed by the University of California, San Francisco, and Harvard University. Extensive collaborations were observed between institutions (Figure 3). The University of Toronto, the University of California, San Francisco, Harvard University, and the University of Washington had high betweenness centrality.

Analysis of reference co-citation

We used all references from the 50 most-cited publications in each successive 3-year grouping to construct each individual network, and then synthesized the individual networks for a total of 243,830 references. We performed reference co-citation analysis to generalize clusters and construct a knowledge map in timeline view, which grouped publications on ARDS treatment into nine major clusters (Figure 4).

The network in this study had a modularity of 0.717, which is typically considered relatively high. We focused on the major clusters that were sorted and tagged by the number of co-cited references. A total of 10 clusters were included in the analysis (Table 3). Three of these clusters (key terms “acute lung injury,” “long-term outcome,” and “extracorporeal membrane oxygenation”) have been active in recent years.

The timeline view of reference Co-citation analysis (Figure 4) shows that the duration of research into extracorporeal membrane oxygenation was the longest, lasting from 2006 to 2018. The use of nitric oxide in treatment was no longer a topic of research papers after 1999. Some references were included in

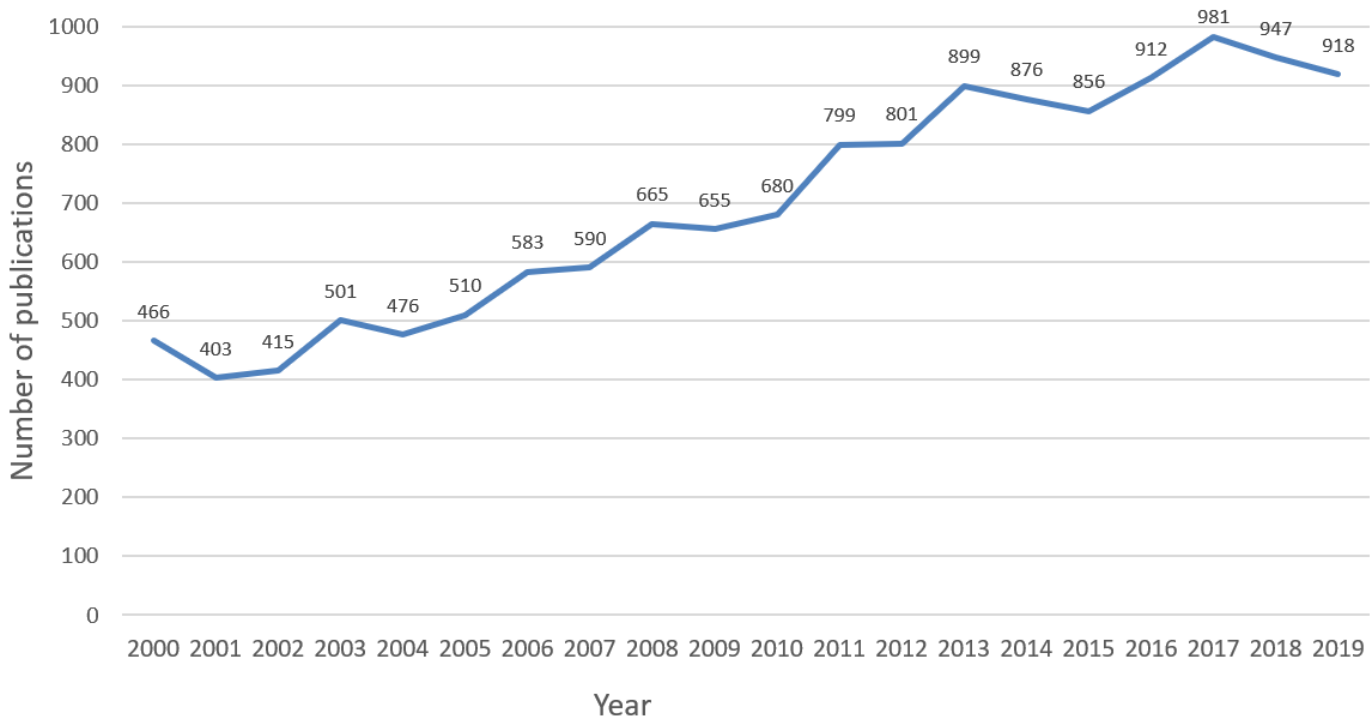


Figure 2: Numbers of articles on acute respiratory distress syndrome published over time.

Table 1: The 10 journals publishing the most research articles on the treatment of acute respiratory distress syndrome.

Journal	N (%)	Country	Impact factor in 2019
Critical Care Medicine	956 (6.86%)	United States	7.598
Intensive Care Medicine	601 (4.31%)	United States	17.44
American Journal of Respiratory and Critical Care Medicine	479 (3.44%)	United States	21.405
Critical Care	460 (3.30%)	Britain	9.097
American Journal of Physiology-Lung Cellular and Molecular Physiology	309 (2.22%)	United States	5.464
Respiratory Care	260 (1.87%)	United States	2.258
Chest	254 (1.82%)	Netherlands	9.41
Current Opinion in Critical Care	200 (1.44%)	United States	3.687
Journal of Critical Care	200 (1.44%)	United States	3.425
Shock	195 (1.40%)	United States	3.454

N (%), number of articles published by the journal and percentage of the total articles assessed in this study. Country refers to the country associated with the publisher. Impact factors are derived from *Journal Citation Reports* (2019) published by the Institute for Scientific Information of the United States.

multiple clusters, acting as a link. Table 4 lists the core articles in the main Co-citation clusters.

Analysis of burst keywords

Keyword co-occurrence analysis returned 59 keywords. The keyword citation burst (citation increase over a given period) identified 15 keywords with strong citation bursts over the past decade (Table 5). Extracorporeal membrane oxygenation, listed in both full and abbreviated forms, was an area of active research between 2013 and 2018. Meta-analysis and randomized controlled trials also had high burst strength, especially meta-analysis in recent years. Two active keywords related to basic ARDS research were NF-kappa B, a key nuclear transcription factor regulating inflammatory responses in ARDS,^[20] and oxidative stress. Recruitment, protective ventilation, and noninvasive ventilation were often-used keywords connected to ARDS treatment between 2013 and 2016. Keywords relating to pathogenic factors such as risk, infection, pneumonia, and sepsis are still in use.

DISCUSSION

Bibliometric analysis is a useful method for identifying impactful institutions, constructing collaboration networks, and identifying research topics from published literature. In addition, bibliometric analysis may assist investigators in predicting research trends in medical science. We have presented a visual analysis of the research literature into the treatment of ARDS, which revealed the following epistemological characteristics. The body of literature has grown over time, with *Critical Care Medicine* and *Intensive Care Medicine* publishing multiple papers on the topic. Many of the researchers publishing on the topic were affiliated with the University of Toronto, St. Michael's Hospital, the University of Washington, and the University of California, San Francisco. Co-citation analysis grouped the references into eight major co-citation clusters indicating research interests

within the field of ARDS therapy. The 15 keywords thus identified may be helpful in formulating future research.

The growth in the number of publications indicates that an increasing number of researchers were studying ARDS treatments, frequently in collaboration with researchers in other institutions. Nearly one-third of the literature was published in only 10 journals, indicating that ARDS treatment was a major focus of research published by these journals.

Reference co-citation analysis was used to assess the co-citation relevance between papers and to categorize the data into major clusters representing research interests. In our study, the reference network was grouped into eight clearly defined co-citation clusters. Active research in this field appears to be dominated currently by extracorporeal membrane oxygenation and acute lung injury. Extracorporeal membrane oxygenation, as an approach to cardiopulmonary support, has been shown to improve the survival of patients with severe respiratory failure^[21] and was used in influenza A (H¹N¹)-associated ARDS.^[22] Related topics of research discussion were criteria for extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, and long-term outcomes of this approach.^[23,24] However, the most recent study (EOLIA trial) in patients with severe ARDS reported no benefit in terms of 60-day mortality rates.^[25] The ventilatory strategies cluster, which contained the most articles, including comprehensive topics involving the open lung,^[26] PEEP level setting^[27] and fluid-management strategy,^[28] short-term prone positioning, and the burden of ARDS,^[29] has been inactive since 2010. The clusters for long-term outcome and acute lung injury have developed and remain active. In particular, the former was in an inherent relationship with the cluster of ventilatory strategies, and we found some overlapping topics in their core literature, such as PEEP^[30] and prone positioning.^[31] Treatment outcome has always been the focus of attention in research into ARDS and,

Table 2: Ranking of the 15 institutions most active in researching treatments for acute respiratory distress syndrome by number of publications.

Institution	N (%)	Betweenness centrality
University of Toronto	574 (4.28%)	0.29
University of California, San Francisco	395 (2.95%)	0.17
Harvard University	327 (2.44%)	0.15
Massachusetts General Hospital	257 (1.92%)	0.12
University of Pennsylvania	237 (1.77%)	0.07
University of Sao Paulo	229 (1.71%)	0.04
Johns Hopkins University	228 (1.70%)	0.07
Vanderbilt University	217 (1.62%)	0.1
University of Washington	216 (1.61%)	0.14
University of Pittsburgh	210 (1.57%)	0.09
University of Milan	203 (1.52%)	0.02
University of Michigan	201 (1.5%)	0.03
St. Michael's Hospital	195 (1.46%)	0.09
University of Colorado	179 (1.34%)	0.08
Mayo Clinic	170 (1.27%)	0.03

N (%), number of articles and percentage of the total articles assessed in this study. Betweenness centrality is a quantitative indicator of the influence of institutions in a collaborative network of academic institutions.

perhaps for this reason, the long-term outcome cluster kept in close contact with the acute lung injury cluster and extracorporeal membrane oxygenation, serving as a bridge between the clusters. The core articles targeting prognosis of ARDS were contained in the aforementioned clusters. From a timeline view, “acute lung injury” was the most recent cluster, and is still active. The themes of core articles included ventilator-induced lung injury,^[32] investigation of ARDS sub-phenotypes,^[33] driving pressure,^[34] the effect of high-flow oxygen on acute hypoxemic respiratory failure,^[35] and the reassessment of ARDS burden.^[1] These topics appeared to be unfocused but involved basic data, issues of wide concern, and investigations in new directions, which were often co-cited in the papers to provide basic support and guidance and probably developed over time.

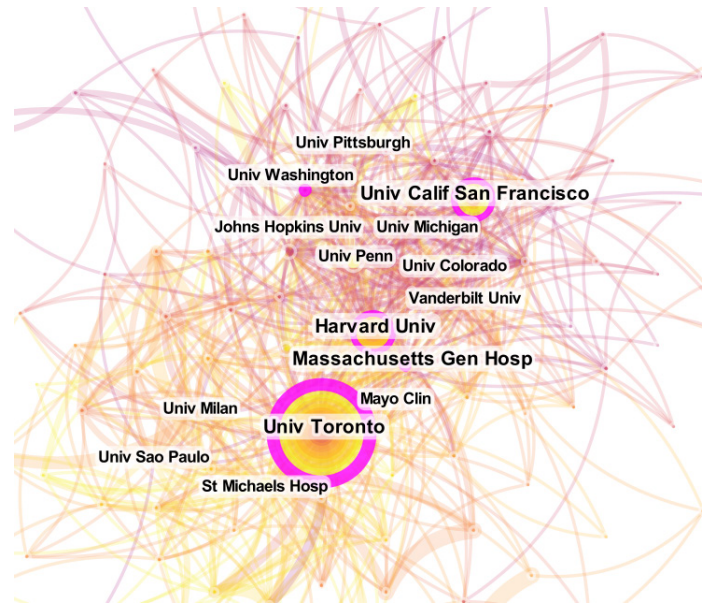


Figure 3: Map of institutions active in publishing research on the treatment of acute respiratory distress syndrome between 2000 and 2019. Larger typeface indicates a larger number of articles published by researchers affiliated with the institution. Core institutions are marked with a purple ring and greater width of the ring indicates high centrality. The thickness of the curve in connecting lines represents collaborative intensity between institutions, with thicker lines denoting more intense collaborations.

A heavily cited keyword is considered an indicator of a topic of research interest or of an emerging trend. Extracorporeal Membrane Oxygenation and its abbreviation (ECMO) were first and second in the ranking of citation burst strength in recent years, indicating that this topic will continue to be studied. Meta-analysis can comprehensively assess the results of previous randomized controlled trials on ARDS to arrive at objective conclusions, and it is expected to be the popular research methodology from the strength value obtained. In the field of basic research, oxidative stress has become a popular topic of investigation in ARDS therapy. Table 5 shows the progress in ARDS research through the evolution of burst keywords over the past decade. Factors that can precipitate ARDS and appeared in the literature we analyzed were pneumonia, infection, and severe sepsis, in chronological order. A similar evolution was reflected in the therapeutic methods, from lung recruitment and protective ventilation to noninvasive ventilation to extracorporeal membrane oxygenation. However, ARDS phenotype was not detected by our analysis, perhaps because of the lack of enough supporting literature. This stratifies the heterogeneous syndrome into homogeneous sub-phenotypes with physiology, clinical data, outcomes, biomarkers, or a combination of these.^[36]

The results of the analysis may be applied in a comparatively narrow range. The researchers who conduct studies on ARDS may have grasped some of the contents, which may be more useful for policy makers and funders who seek to understand the current state and trends in the field. To perform the co-citation clustering analysis, we selected Web of Science as our final literature source,

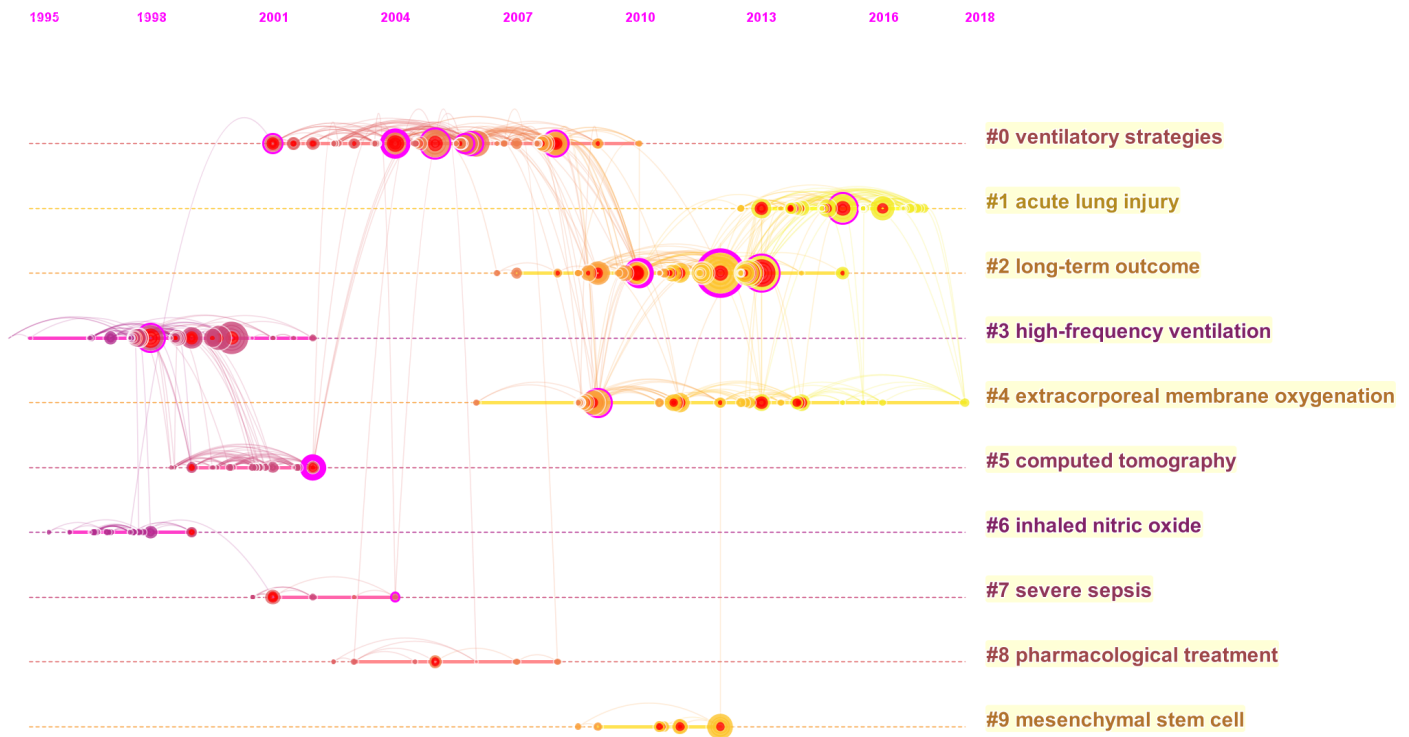


Figure 4: Timeline view of the knowledge map from reference co-citation analysis of research into treatments for acute respiratory distress syndrome published between 2000 and 2019. Ten classified clusters, tagged with characteristic names, are represented by colored line segments and numbered from 0 to 9 (from the largest to smallest number of references). Tag names were assigned by a tag word extraction algorithm (log-likelihood ratio algorithm). The left endpoints of colored horizontal lines indicate the year when co-citation links in the fields appeared for the first time, and their length denotes the duration of publication of relevant research articles. Lines connecting the clusters reflect the co-citation relationship, and often-cited articles are highlighted by dots or rings.

Table 3: Characteristics of co-citation clusters.

Cluster	Size ^a	Beginning year	Ending year	Activity ^b	Tag name ^c
#0	46	2001	2010	inactive	ventilatory strategies
#1	38	2013	2017	active	acute lung injury
#2	37	2007	2015	active	long-term outcome
#3	31	1995	2002	inactive	high-frequency ventilation
#4	27	2006	2018	active	extracorporeal membrane oxygenation
#5	19	1999	2002	inactive	computed tomography
#6	17	1996	1999	inactive	inhaled nitric oxide
#7	7	2001	2004	inactive	severe sepsis
#8	7	2003	2008	inactive	pharmacological treatment
#9	6	2009	2012	inactive	mesenchymal stem cell

^aNumber of published articles. ^bPersistence of a theme over the past 5 years (yes/no). ^cTypical word assigned to represent the main content of the cluster using a log-likelihood ratio algorithm.

which may have excluded some studies. Valuable articles can also be found in evidence-based medicine databases such as the Cochrane Library and citation databases such as Scopus.

We purposely excluded articles related to coronavirus disease 2019 (COVID-19); COVID-19 pandemic of 2020 will inevitably lead to an increase in ARDS treatment studies, but assessing their contribution to the field of ARDS treatment necessitates a hindsight view. The COVID-19 pandemic initiated multiple

studies published in 2020 and 2021 that are related to ARDS and acute lung injury but whose objective was specifically the treatment of coronavirus infection. These investigations were conducted by researchers and clinicians who have not focused on ARDS treatments in the past and whose specific interest when conducting these studies lay in alleviating the symptoms of COVID-19. We therefore judged that including these studies in the body of literature analyzed in the present work would skew

Table 4: Core articles in the main co-citation clusters

Cluster and tag name	Lead author	Publishing year	Theme
#4 ECMO	Peek GJ ^[21]	2009	ECMO, severe adult respiratory failure.
#4 ECMO	Davies A ^[22]	2009	ECMO, influenza A.
#4 ECMO	Bein T ^[23]	2013	Extracorporeal carbon dioxide removal, ultraprotective ventilation.
#4 ECMO	Schmidt M ^[24]	2013	ECMO, outcome assessment.
#0 Ventilatory strategies	Meade MO ^[26]	2008	Open-lung strategy, ARDS.
#0 Ventilatory strategies	Mercat A ^[27]	2008	PEEP setting strategy, ARDS.
#2 Long-term outcome	Briel M ^[30]	2010	Higher versus lower PEEP, ARDS.
#2 Long-term outcome	Papazian L ^[37]	2010	Neuromuscular blocker, ARDS.
#2 Long-term outcome	Ranieri VM ^[38]	2012	Berlin definition, ARDS.
#2 Long-term outcome	Ferguson ND ^[39]	2013	High-frequency oscillatory ventilation, ARDS.
#2 Long-term outcome	Young D ^[40]	2013	High-frequency oscillatory ventilation, ARDS.
#2 Long-term outcome	Guérin C ^[31]	2013	Prone positioning, ARDS.
#1 Acute lung injury	Amato MBP ^[34]	2015	Driving pressure, ARDS.
#1 Acute lung injury	Bellani G ^[1]	2016	Epidemiology, patterns of care, mortality, ARDS.
#1 Acute lung injury	Slutsky AS ^[32]	2013	Ventilator-induced lung injury.
#1 Acute lung injury	Frat JP ^[35]	2015	High-flow oxygen, acute hypoxemic respiratory failure.
#1 Acute lung injury	Calfee CS ^[33]	2014	ARDS subphenotypes.
#0 Ventilatory strategies	Gattinoni L ^[29]	2001	Prone positioning, acute respiratory failure.
#0 Ventilatory strategies	Brower RG ^[41]	2004	Higher versus lower PEEP, ARDS.
#0 Ventilatory strategies	Rubenfeld GD ^[42]	2005	Incidence and outcomes, acute lung injury.
#0 Ventilatory strategies	Wiedemann HP ^[28]	2006	Fluid-management strategy, acute lung injury.

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure.

Table 5: Keywords with the strongest citation burst in papers on treatment of acute respiratory distress syndrome over the past two decades.

Keyword	Strength	Beginning year	Ending year
Extracorporeal membrane oxygenation	67.91	2013	2018
ECMO	54.72	2015	2018
Meta-analysis	50.56	2015	2018
Oxidative stress	31.35	2015	2018
Noninvasive ventilation	29.57	2015	2016
Risk factor	29.35	2009	2014
Randomized controlled trial	27.84	2009	2010
Infection	27.54	2011	2012
Protective ventilation	17.35	2013	2014
NF-kappa B	13.44	2013	2018
Survival	12.37	2013	2014
Recruitment	10.06	2013	2014
Randomized controlled trial	7.4	2013	2015
Pneumonia	7.11	2009	2011
Severe sepsis	6.62	2013	2016

Strength denotes the rate of increase in citations over a given period. Higher strength values denote more active research. ECMO, extracorporeal membrane oxygenation.

the findings away from the true numbers of research institutions and journals that maintain a long-term and consistent focus on ARDS treatment strategies. However, we speculate that the next few years would witness a trend in researching specific aspects of viral-induced ARDS. Research topics that are deemed exciting are often pursued intensively during a given period and result in multiple publications, but the findings may not be clinically valuable with the passage of time and further investigation, weakening the value of the research topic. In addition, the pursuit of these topics typically lasts only as long as research funders are interested in offering funds for such investigations. The present work provides a pre-COVID baseline that could be used as a comparison benchmark in future bibliometric analyses. Finally, we did not include conference abstracts in our search, which may have influenced the weighting of results.

CONCLUSION

On the basis of the bibliographic analysis of the literature published in the past 20 years, research into ARDS treatment has been continuous. Extracorporeal membrane oxygenation is currently a topic of active research, and it and oxidative stress are likely to remain the focus in the near future. Meta-analysis of original studies will still be a popular research method in this field.

AUTHORS' CONTRIBUTIONS

Z.Y.W. designed the study and manuscript content and contributed to drafting the manuscript. Z.C.Z. contributed to the manuscript content, collected and analyzed the data, and drafted the manuscript. J.Z. and Z.K.C. contributed to the manuscript content. X.Z. contributed to the study concept and critical evaluation of the manuscript. All authors approved the submission of this version for publication.

ACKNOWLEDGEMENT

This study was funded by the National Science and Technology Major Project (grant number 2018ZX10101004), The capital health research and development of special (grant number 2020-2-4094), Beijing Natural Science Foundation (grant number 7212130), and Peking University Third Hospital Foundation (grant number Y76478-01).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ARDS: Acute respiratory distress syndrome; **PEEP:** Positive end-expiratory pressure; **ECMO:** Extracorporeal membrane oxygenation; **COVID-19:** Coronavirus disease 2019.

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Cite this article: Wang ZY, Zhou ZC, Zheng J, Cong ZK, Zhu X. Bibliometric Analysis of Literature on Acute Respiratory Distress Syndrome Treatments Published Between 2000 and 2019. *J Scientometric Res*. 2023;12(2):422-30.