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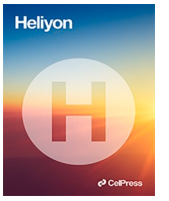

Research article

Research hotspots and evolving trends of barrier dysfunction in acute lung injury and acute respiratory distress syndrome

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ABSTRACT

Endothelial and epithelial barrier dysfunction due to increased permeability and heightened inflammatory reactions influences the emergence of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Nevertheless, bibliometric research comparing endothelial and epithelial barriers is limited. Therefore, this bibliometric study analyzed the Web of Science Core Collection (WoSCC) of the Science Citation Index Expanded literature to explore present research priorities and development tendencies within this field. We conducted a comprehensive search (October 18, 2023) on WoSCC from January 1, 2010, to October 18, 2023, focusing on articles related to endothelial and epithelial barriers in ALI and ARDS. Retrieved data were visualized and analyzed using R-bibliometrix, VOS viewer 1.6.19, and CiteSpace 6.2. R4. Functional enrichment analysis of gene targets identified in the keyword list using Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene ontology databases, and based on the STRING database to construct a PPI network to predict core genes. A total of 941 original articles and reviews were identified. The United States had the highest number of publications and citations and the highest H-index and G-index. According to the Collaboration Network Analysis graph, the United States and China had the strongest collaboration. Birukova AA had the most publications and citations among all authors, while eight of the top ten institutions with mediator centrality were located in the United States. The *American Journal of Physiology-Lung Cellular and Molecular Physiology* was the leading journal and had the most well-established publication on endothelial and epithelial barriers in ALI and ARDS. Bibliometric analysis revealed that the most frequently used keywords were acute lung injury, ARDS, activation, expression, and inflammation. RHOA appeared most frequently among gene-related keywords, and the PI3K-AKT signaling pathway had the highest count in KEGG pathway enrichment. Research on endothelial versus epithelial barriers in ALI and ARDS remains preliminary. This bibliometric study examined cooperative network connections among countries, authors, journals, and network associations in the cited references. Investigation of the functions of the endothelial and epithelial barriers in ALI/ARDS associated with COVID-19 has recently gained significant attention.

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1. Introduction

Acute respiratory distress syndrome (ARDS) is characterized by acute and widespread inflammation of the lungs, causing an increase in blood vessel permeability and lung weight and loss of aerated lung tissue [1]. Clinically, ARDS is characterized by arterial hypoxemia, increased shunting, associated bilateral X-ray turbidity, increased alveolar inefficiency, decreased lung compliance [2], and high histological heterogeneity, including alveolar edema, capillary congestion, and hyaline membrane formation [3]. Prone ventilation enhances lung uniformity, improves the air distribution-to-blood flow ratio, aligns the lung with the chest wall, minimizes stress and strain, and lowers the likelihood of ventilator-induced lung injury (VILI) [4]. Dysfunction of the endothelial barrier and epithelium, marked by increased permeability and inflammatory reactions, is implicated in the development of acute respiratory conditions, such as ARDS and sepsis, and chronic ailments, including pulmonary hypertension and interstitial lung diseases [4–6]. Alveolar epithelial cells are closely linked to endothelial cells in the lungs, creating an epithelial-endothelial or alveolar-capillary barrier [7]. Furthermore, the inner epithelial cells and their merged basement membranes form an extremely thin layer (<1 μm) that facilitates the swift and effective exchange of gases between the alveoli and blood vessels while preventing the inhalation of particles and microorganisms and playing a vital role in maintaining the dynamic equilibrium between tissues and organs [8,9]. Mechanical ventilation is an indispensable and life-preserving measure for patients with ARDS, although it can exacerbate inflammatory reactions, intensify pulmonary endothelial barrier and epithelial dysfunction, and contribute to mortality [8,10]. Although research on the role of the endothelial barrier in acute lung injury (ALI) and ARDS has progressed, the remaining knowledge gaps warrant further research.

Bibliometric analysis employs both qualitative and quantitative approaches to objectively and visually examine scientific literature, effectively showcasing the progress of research and aiding in predicting its current state and future directions [11]. While offering an overview and predicting future advancements in a particular area of research, bibliometric analysis also assesses the contributions of different authors, institutions, countries, and journals [12,13]. Although bibliometric analyses are used in various areas of medical research, bibliometric studies comparing the endothelial and epithelial barriers in ALI/ARDS are scarce. Therefore, this bibliometric investigation visually examined and analyzed scholarly works from the Web of Science Core Collection (WoSCC) to provide a comprehensive perspective and guide future comparative research on endothelial and epithelial barriers in ALI/ARDS.

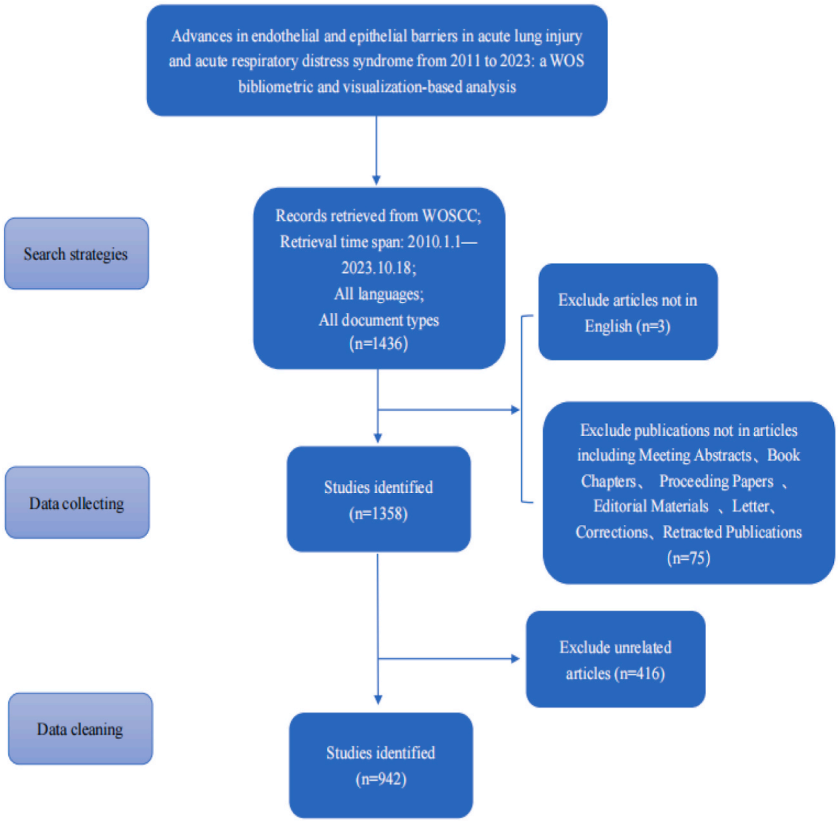


Fig. 1. Detailed literature screening process.

2. Materials and methods

2.1. Data sources and retrieval

We systematically searched the WoSCC database on October 18, 2023, by entering the search terms ((((TS=(ALI)) OR TS= (Acute lung injury)) OR TS=(ARDS)) OR TS= (Acute respiratory distress syndrome)) AND ((TS= (Endothelial barrier)) OR TS= (Epithelial barrier)), which were set from January 1, 2010, to October 18, 2023. Both authors (Zixin Luo and Duoqin Huang)conducted data searches and sorting by reviewing titles, reading complete abstracts if needed, and engaging in discussions when there were disagreements. This resulted in a final agreement of 90 %, indicating significant concurrence. We excluded non-English articles and restricted the publication type to reviews and original articles. Finally, 941 articles were identified (Fig. 1).

2.2. Bibliometric analysis

Initially, the WoSCC database was used to extract raw data, resulting in a comprehensive record and references that included the number of articles and citations, H-index and G-index, year of publication, country, affiliation, authors, journals, references, and keywords [14–16]. The information was exported as a TXT file into R-4.3.1 software created by Robert Gentleman and Ross Ihaka at the University of Auckland, New Zealand for an initial examination. Subsequently, the organized information was assessed using Bibliometrix, CiteSpace 6.2. R4 (created by Chaomei Chen from Drexel University, Dalian, China), and VOS viewer v.1.6.19 (developed by Van Eck and Waltman from the Centre for Science and Technology Studies, Netherlands) for visualized analysis. Functional enrichment analysis of gene targets identified in the keyword list using KEGG and GO databases. PPI (protein-protein interaction) research using the STRING online database.

VOS viewer and CiteSpace are important software packages for analyzing and visualizing bibliometric data [11]. CiteSpace is a citation visualization software based on Java [17] that provides a platform for exploring new ideas and comparing different methods. It can analyze literature from various perspectives, identify research hotspots and trends, and present them visually, aiding researchers in understanding field developments [18,19]. We utilized CiteSpace to overlay journal maps, conducted a co-occurrence analysis of co-cited articles from institutions to determine citation strength and keyword bursts, and created a timeline axis for keywords [20,21]. VOS viewer is a Java-based tool that examines a substantial volume of literary information [22] and generates a map for creating keyword co-occurrences and clustering mappings based on textual data [23]. Bibliometrix, developed by Massimo Aria and Corrado Cuccurullo, is a freely available R tool [24] that enables comprehensive analysis using the R package (R-4.3.1-win).

2.3. Bioinformatics analysis

GO and KEGG analyses as computational methods for assessing genetic functions and biological pathways. Visualization of enrichment analysis results using the ggplot2 package based on R (4.2.1). In this study, a PPI network for predicting core genes was constructed using a list of differential genes entered into the STRING database (minimum required interaction score> 0.9).

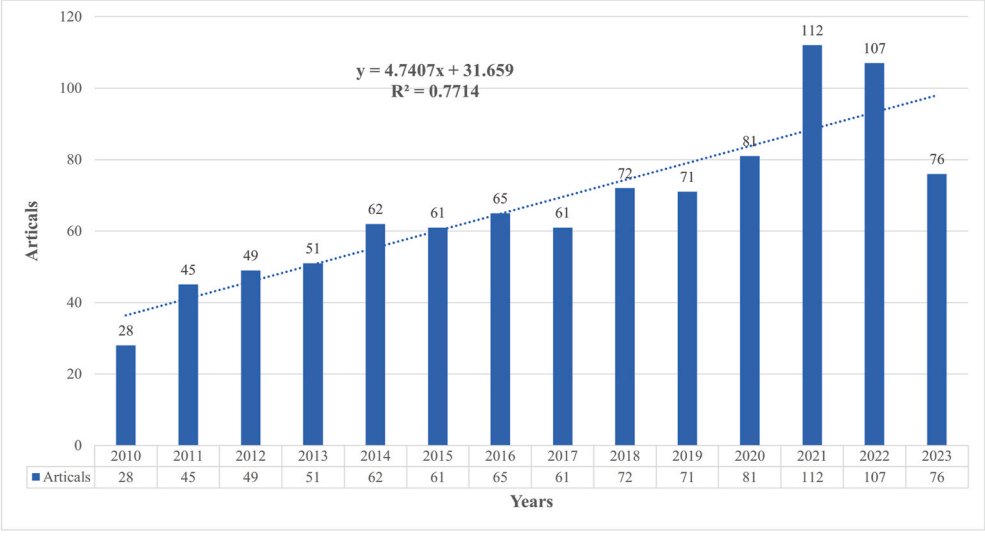


Fig. 2. Global Trends on Endothelial Barrier and Epithelial Barrier in ALI/ARDS Publications. The bar chart shows the global trend in publication growth from 2010 to 2023. The curve shows the model-fit curve for the growth trend in publications.

3. Results

3.1. Global publication trend

We identified 941 publications comparing the endothelial and epithelial barriers in ALI and ARDS from 2010 to 2023. The annual publication count showed a growth trajectory from 28 in 2011 to 107 in 2022, and the annual growth trend fit the fitted curve $y = 4.7407x + 31.659$. The annual number of publications (NP) showed a strong correlation with the year of publication, with a correlation coefficient (R^2) of 0.7714 (Fig. 2). Notably, since 2020, there has been a substantial increase in the number of published studies. The growing attention regarding the subject of endothelial and epithelial barriers in ALI/ARDS suggests a potential trajectory for long-term research.

3.2. Contribution of countries

Forty-three countries had engaged in research on endothelial and epithelial barriers in ALI/ARDS; most of them were Asian. The United States (435 publications) was the most productive country, followed by China (283 publications), Germany (54 publications), Canada (25 publications), and Japan (23 publications). The United States also had the highest H-index and G-index values, demonstrating its high level of influence in the field, as shown in Table 1. The area map illustrating the annual cumulative number of publications for the top ten countries reveals a significant increase in China's annual cumulative number of publications, from 5 in 2010 to 283 in 2023, reducing the gap between it and the United States, as depicted in Fig. 3A. Fig. 3B displays the top five countries in terms of total citations, namely the United States (14,218), China (4,880), Germany (2,541), Canada (849), and Netherlands (716). Collaboration between countries was visualized using VOS viewer, which analyzes the collaboration of co-authors from countries with over five publications in this area. The analysis included 20 countries (Fig. 3C). The size of the nodes in the Figure indicates the number of publications, while the thickness of the connecting lines represents the strength of the connection relative to the total link strength. The United States ranked first in total link strength (175), followed by Germany (93), China (75), the United Kingdom (39), and Canada (36). Many countries did not have cooperative relationships with other countries, and countries should increase cooperation and exchanges to enhance cooperative relationships.

3.3. Contribution of authors

As shown in Fig. 4A, we identified 84 authors who collaborated with other authors in more than six publications. After excluding 15 authors who were not connected, 69 instances of author collaboration were found. The three leading authors with the highest overall connections were Birukova AA (total link strength = 135), Garcia JGN (116), and Birukov KG (114) (Fig. 4B). A co-citation relationship refers to when at least two authors are cited simultaneously in one or more subsequent papers [25]. Of 258,580 co-cited authors, 34 were selected after restricting the number of citations to 50. The remarkable link strength between Birukov KG and Birukova AA (682 citations) indicates a potential similarity in their research topics (Table 2). Birukova AA had the highest publication count and H-index, whereas Garcia JGN had a higher G-index and number of citations than Birukova AA. This suggests that these authors held a significant influence in the field.

3.4. Contribution of journals

A total of 294 journals published 941 papers focusing on endothelial and epithelial barriers in ALI/ARDS. Table 3 lists the number of studies on ALI/ARDS-related endothelial and epithelial barriers and their impact metrics (H-index, G-index, IF, and JCR partitioning), along with the top 10 journals based on the number of published articles. Authors are encouraged to concentrate on these journals, as they are more likely to publish articles on research concerning endothelial and epithelial barriers. *American Journal of Physiology-Lung Cellular and Molecular Physiology* (93 articles, impact factor [IF] = 4.9) had the highest number of articles, followed by *American Journal of Respiratory Cell and Molecular Biology* (47 articles, IF = 6.4), *Plos One* (30 articles, IF = 3.7), *Frontiers in Immunology* (28 articles, IF = 7.3), and *Frontiers in Physiology* (20 articles, IF = 4.0). Fig. 5A shows that *American Journal of Physiology-Lung Cellular*

Table 1
Top 10 countries with the most publications on Endothelial and Epithelial Barriers in Acute Lung Injury and Acute Respiratory Distress Syndrome.

Rank	Country	No. of documents	Total Citations	Average Article Citations	H-index	G-index
1	USA	435	14218	32.70	51	76
2	CHINA	283	4880	17.20	35	49
3	GERMANY	54	2541	47.10	20	33
4	CANADA	25	849	34.00	15	23
5	JAPAN	23	563	24.50	10	19
6	NETHERLANDS	13	716	55.10	7	11
7	UNITED KINGDOM	13	584	44.90	9	11
8	ITALY	11	280	25.50	7	11
9	FRANCH	10	274	27.40	8	9
10	BRAZIL	9	315	35.00	5	8

Fig. 3. National contributions to the study of endothelial versus epithelial barriers in acute lung injury and acute respiratory distress syndrome **(A)** Statistical chart of the annual cumulative number of publications for the top 10 countries in terms of number of publications **(B)**Citation statistics for the top 10 countries **(C)**National Co-authorship Analysis Chart.

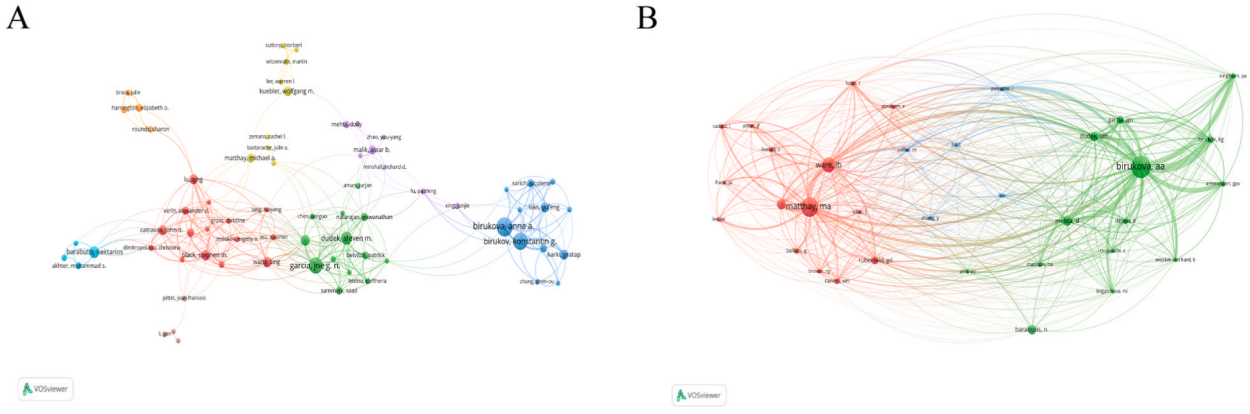


Fig. 4. Author analysis chart of studies involving endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome **(A)** Collaborative network map of 84 authors with more than 6 articles **(B)**VOSviewer visualization of co-citing authors.

and Molecular Physiology had the highest citation frequency (3,437), followed by *American Journal of Respiratory Cell and Molecular Biology* (2,650). In summary, *American Journal of Physiology-Lung Cellular and Molecular Physiology* has made important contributions in this field. Chen and Leydesdorff developed a dual-map overlay that illustrates the spread of literature within specific disciplines. The

Table 2
Top 10 most published authors on endothelial barrier and epithelial barrier in acute lung injury and acute respiratory distress syndrome.

Rank	Author	NP	TC	H-index	G-index
1	BIRUKOVA AA	44	1135	21	32
2	GARCIA JGN	39	1266	19	35
3	BIRUKOV KG	38	1034	20	31
4	DUDEK SM	28	632	13	25
5	BARABUTIS N	21	375	11	19
6	BLACK SM	19	466	13	19
7	JACOBSON JR	19	529	11	19
8	WANG T	17	320	10	17
9	KUEBLER WM	16	1669	13	16
10	CATRAVAS JD	16	537	12	16

Table 3
Top 10 journals in terms of number of articles published on endothelial barrier and epithelial barrier in acute lung injury and acute respiratory distress syndrome.

Rank	Journal	NP	TC	H-index	G-index	IF (2022)	JCR (2022)
1	American Journal of Physiology-Lung Cellular and Molecular Physiology	93	3437	38	54	4.9	Q2
2	American Journal of Respiratory Cell and Molecular Biology	47	2650	27	47	6.4	Q1
3	Plos One	30	807	18	28	3.7	Q2
4	Frontiers in Immunology	28	580	15	24	7.3	Q1
5	Frontiers in Physiology	20	130	7	11	4.0	Q2
6	Scientific Reports	20	407	11	20	4.6	Q2
7	Shock	19	349	11	18	3.1	Q3
8	International Journal of Molecular Sciences	18	437	9	18	5.6	Q1
9	International Immunopharmacology	17	255	9	15	5.6	Q1
10	Respiratory Research	17	483	11	17	5.8	Q1

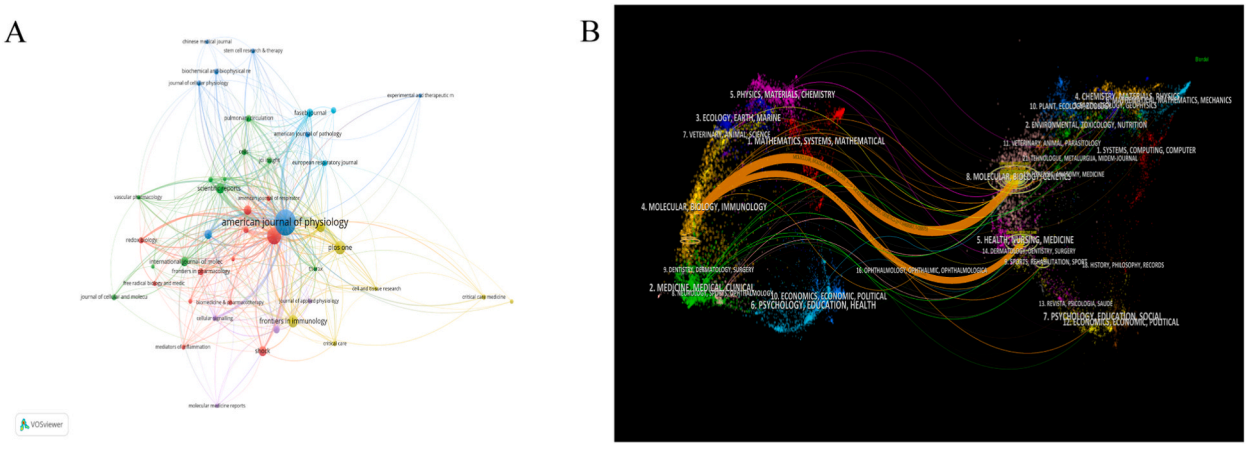


Fig. 5. Articles published in different journals on endothelial versus epithelial barriers in acute lung injury and acute respiratory distress syndrome. **(A)**Network map between 45 journals with more than 5 articles, with the size of the nodes representing the number of articles and the links between the nodes representing the strength of citations.**(B)**Double map overlay of citation relationships of endothelial barrier and epithelial barrier articles in acute lung injury and acute respiratory distress syndrome. Citing journals are shown on the left, cited journals on the right, and citation relationships are indicated by colored paths.

term 'dual-map' refers to a map of the cited and quoted components of the overall visualization, which shows the disciplinary concentration of articles and how they connect regions on the global map through citation links [26,27]. The dual-map overlay for ALI/ARDS shows the citing journals on the left and cited journals on the right. The labels in the middle of the cluster indicate the corresponding disciplines of the cited journals. The colored curves represent the paths of the references originating from the citation maps on the left side. We used the z-score function to highlight connections and improve clarity and identification [28]. In this dual map, there is a prominent citation path, with the most significant and primary source disciplines easily identifiable as (1) molecular/biology/genetics and (2) health/nursing/medicine. Most citation links are directed towards disciplines, such as molecular, biology, or immunology (Fig. 5B).

3.5. Co-occurrence analysis of institutions

The co-occurrence graph in Fig. 6, generated using CiteSpace, displays the institutions associated with the studies on endothelial and epithelial barriers in ALI/ARDS. Each node represents an institution; larger nodes represent institutions that are cited more often. Links between nodes represent collaboration between institutions, with the color and thickness representing the duration and intensity of the collaboration, respectively. *The University of Illinois System* ranked first in terms of number of citations (n = 82), followed by *the University of Illinois Chicago* (n = 80), the *Veterans Health Administration* (n = 55), the *US Department of Veterans Affairs* (n = 55), and the *University of Chicago* (n = 50). Table 4 lists the top 10 institutions based on their intermediary centrality. CiteSpace refers to nodes with intermediary centrality >0.1 as key nodes; the three agencies with the highest intermediary centrality were *Veterans Health Administration* (Centrality = 0.15), *US Department of Veterans Affairs* (Centrality = 0.15), and *University of California System* (Centrality = 0.13). These agencies have made important contributions to the field. Among the top 10 institutions in terms of mediator centrality, 8 were in the United States.

3.6. Keyword analysis

The keywords illustrated in Fig. 7A occurred over 17 times in the analysis; a total of 88 keywords were categorized into four clusters, each of which is represented by a distinct color. The main components of Clusters 1 and 2 were "Acute Lung Injury", "Respiratory-Distress- Syndrome", "Alveolar Epithelial-Cells", "Barrier Dysfunction", and "COVID-19". Disruption and impairment of the barrier function of the alveolar epithelium and microvascular endothelial cells are vital predisposing elements for lung damage and ARDS resulting from influenza virus infection. The keywords in Clusters 3 and 4 were mainly "Inflammation", "Activation", "Expression", and "Cells", emphasizing the activation of inflammatory response and ALI/ARDS in the relationship between the endothelial and epithelial barriers. The keywords in Fig. 7B were color-coded by VOS viewer based on the average time of their appearance; purple represents earlier appearances, while yellow represents more recent appearances. The average year of publication (APY) showed that the most recent keywords were "COVID-19" (Cluster 2, 2021.13), "SARS-COV-2" (Cluster 2, 2021.04), and "Mortality" (Cluster 4, 2019.23), which were associated with the endothelial and epithelial barrier in treated patients with COVID-19. Furthermore, functions such as "Growth-Factor", "Gene-Expression", and "Vascular-Permeability" are gaining more attention in comparison to "Autophagy", "Stem-Cells", and "Adhesion". CiteSpace clusters closely related keywords and extracts only the top ten clusters. Each cluster is represented by the keyword with the highest log-likelihood ratio (LLR); the higher the LLR, the more representative the cluster. The modularity value (Q) in Fig. 7C was 0.3974, and the average contour value of the network (S) was 0.721. Q > 0.3 indicates a significant cluster structure. When S > 0.5, clustering is plausible; S > 0.7 indicates convincing clustering, with fewer clusters resulting in larger cluster sizes [22,29,30]. CiteSpace generates a visual timeline axis for keywords in clusters to track keyword evolution. A few of the more active clusters in the early years included # acute lung injury, #alveolar epithelial cells, and # mechanical

Fig. 6. Institutional co-occurrence analysis maps on endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome.

Table 4
Top 10 Affiliation in mediated centrality on endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome.

Rank	Affiliation	Freq	Degree	Centrality	Country
1	Veterans Health Administration (VHA)	55	63	0.15	USA
2	US Department of Veterans Affairs	55	63	0.15	USA
3	University of California System	43	57	0.13	USA
4	University of Illinois System	82	56	0.09	USA
5	University of Chicago	50	41	0.08	USA
6	CIBER - Centro De Investigacion Biomedica En Red	12	21	0.08	SPAIN
7	Justus Liebig University Giessen	20	31	0.07	GERMANY
8	Vanderbilt University	6	31	0.07	USA
9	University of Illinois Chicago	80	52	0.06	USA
10	Indiana University System	12	25	0.06	USA

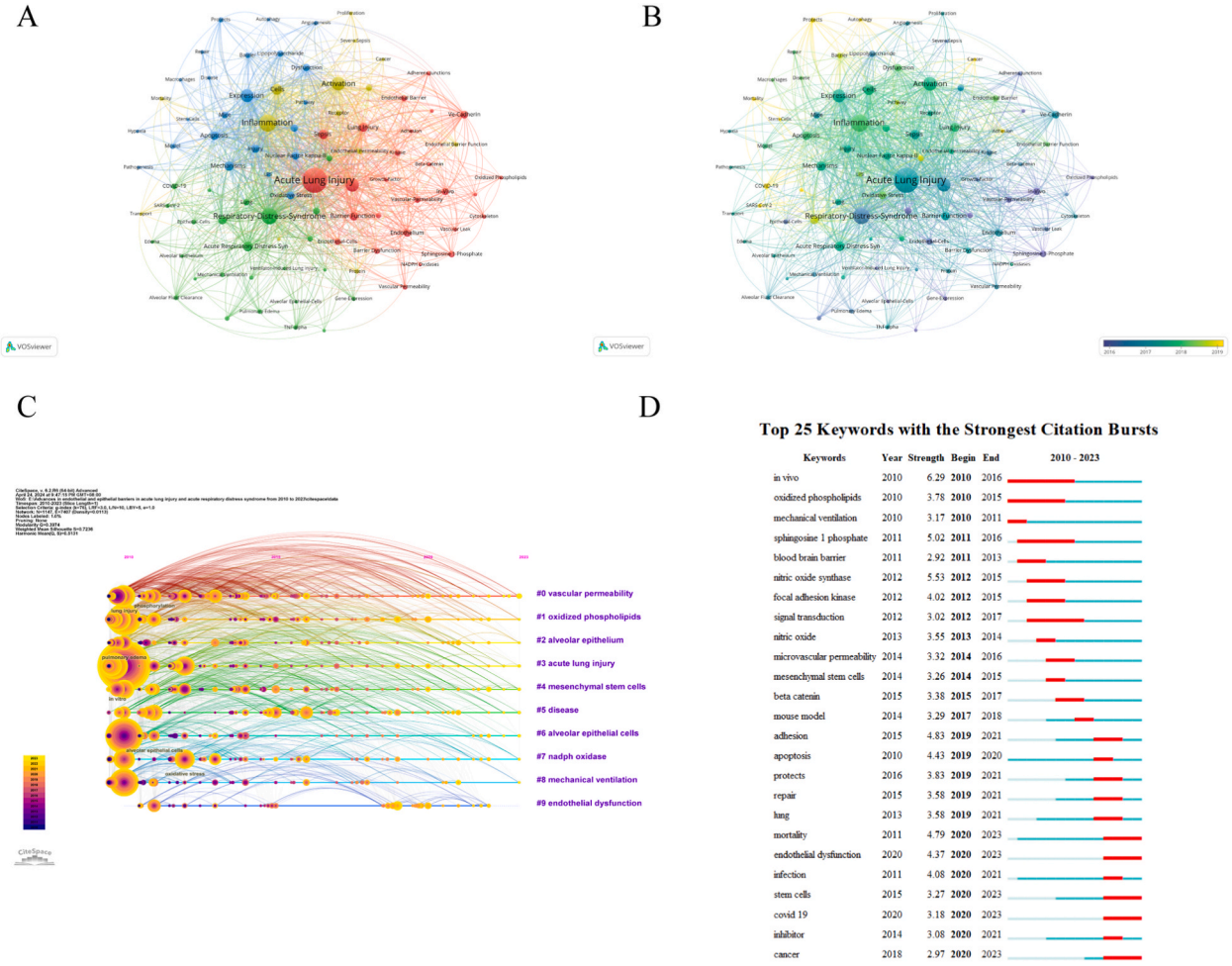


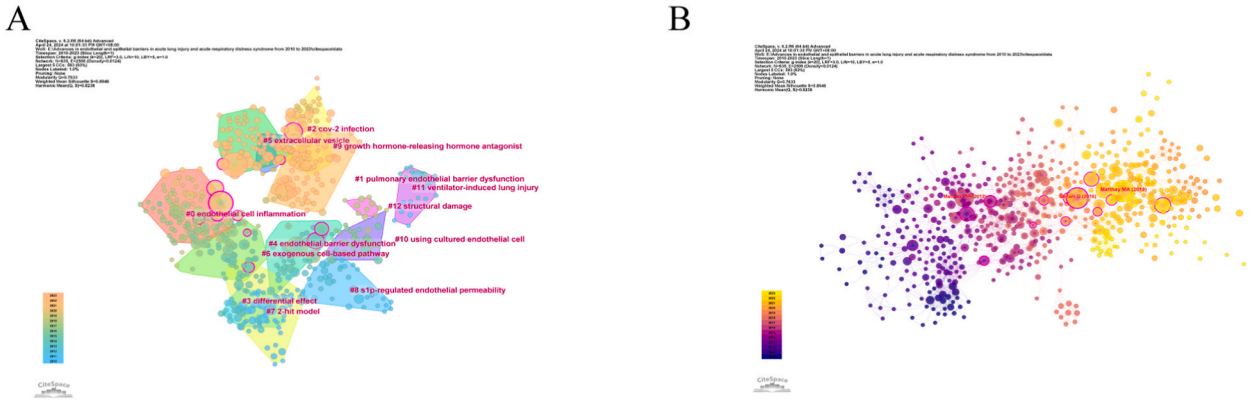
Fig. 7. Co-occurrence keyword analysis of endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome. **(A)**Visual analysis of 88 keywords with more than 17 occurrences in VOSviewer **(B)**Timeline visualization of keywords **(C)**Timeline chart of the top 10 keyword clusters produced by CiteSpace **(D)** Top 25 keywords for the strongest citation bursts.

ventilation. #Vascular permeability and #mesenchymal stem cells have been more active in recent years, and may be hotspots for research (Fig. 7C). Fig. 7D displays the top 25 keywords with the most prominent citation bursts. The timeline is represented by a non-continuous blue line, where each small blue rectangle represents a span of 1 year. The red portion of the timeline indicates the period during which bursts of keywords occurred [31]. The peak intensity of "in vivo" outbreaks highlights its crucial involvement in the advancement of the field. Furthermore, keywords with a higher intensity in recent outbreaks included "mortality", "stem cells", "cancer", and "covid 19". This suggests that these keywords have gained increasing attention in recent years and will dominate reserach areas in the future. We analyzed 343 animal research articles using CiteSpace for keyword timeline graphs. The timeline

graph categorized the keywords into nine clusters; the more active clusters in the early period were #in vivo, #oxidative stress, and #respiratory distress syndrome. The more active clusters in the latter period were #alveolar epithelium, and #neutrophil extracellular traps, suggesting that the field is shifting to more in-depth molecular mechanism research (Supplemental Fig. 1).

3.7. Analysis of co-cited references

Co-cited references refer to articles cited collectively in other publications [32]. Fig. 8A shows that CiteSpace classified co-cited references into the following 13 clusters: #endothelial cell inflammation, #plumonary endothelial barrier dysfunction, #cov-2 infection, #differential effect, #endothelial barrier dysfunction, #extracellular vesicle, #exogenous cell-based pathway, #2-hit model, #S1p-regulated endothelial permeability, #growth hormone-releasing hormone antagonist, #using cultured endothelial, #ventilator-induced lung injury, and #structural damage. Table 5 lists the 10 most frequently mentioned sources, with two associated with COVID-19, indicating the significant influence of COVID-19 on the endothelial-epithelial barrier. Fig. 8B illustrates the cited references. The graph contains nodes representing cited references, and the size of each node reflects the number of co-citations. Co-citation relationships are represented by lines connecting the nodes. Additionally, the chart features a gradient of colors ranging from purple to yellow, symbolizing various years from 2011 to 2023 (Fig. 8C). We obtained 96 highly cited references using CiteSpace (selection criteria: top 25; number of states: 2; minimum duration: 2). A citation surge of great intensity refers to a sudden surge in the number of references to an article within a specific timeframe to pinpoint emerging subjects and areas of research with considerable interest in associated disciplines [33]. A study titled "RAB26-dependent autophagy protects adherens junctional integrity in acute lung injury", published in 2018, has been frequently cited in recent years (2021–2023). The authors of this study highlighted that RAB26-SRC signaling activation provides a new therapeutic opportunity to prevent vascular leakage in ALI [34]. More importantly, their study provides a critical foundation for the continued exploration of endothelial/epithelial barriers in ALI/ARDS.



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Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2010 - 2023
Matute-Bello G, 2008, AM J PHYSIOL-LUNG C, V295, PL379, DOI 10.1152/ajplung.90010.2008, DOI	2008	9.83	2010	2013	
Mehta D, 2006, PHYSIOL REV, V86, P279, DOI 10.1152/physrev.00012.2005, DOI	2006	5.97	2010	2011	
Matthay MA, 2011, ANNU REV PATHOL-MECH, V6, P147, DOI 10.1146/annurev-pathol-011110-130158, DOI	2011	8.52	2011	2016	
Wray C, 2009, AM J PHYSIOL-LUNG C, V297, PL219, DOI 10.1152/ajplung.00043.2009, DOI	2009	5.97	2011	2013	
Ganter MT, 2008, CIRC RES, V102, P804, DOI 10.1161/CIRCRESAHA.107.161067, DOI	2008	5.38	2011	2012	
Matute-Bello G, 2011, AM J RESP CELL MOL, V44, P725, DOI 10.1165/rcmb.2009-0210ST, DOI	2011	7.83	2012	2016	
Crosby LM, 2010, AM J PHYSIOL-LUNG C, V298, PL715, DOI 10.1152/ajplung.00361.2009, DOI	2010	6.03	2012	2015	
Ranieri VM, 2012, JAMA-J AM MED ASSOC, V307, P2526, DOI 10.1001/jama.2012.5669, DOI	2012	7.55	2013	2017	
Matthay MA, 2012, J CLIN INVEST, V122, P2731, DOI 10.1172/JCI60331, DOI	2012	19.47	2014	2017	
Birukova AA, 2012, AM J PHYSIOL-LUNG C, V302, PL965, DOI 10.1152/ajplung.00292.2011, DOI	2012	6.24	2014	2016	
Birukova AA, 2010, AM J PHYSIOL-LUNG C, V298, PL837, DOI 10.1152/ajplung.00263.2009, DOI	2010	5.38	2014	2015	
Tauseef M, 2012, J EXP MED, V209, P1953, DOI 10.1084/jem.20111355, DOI	2012	5.27	2014	2016	
Dabrowski O, 2013, LAB INVEST, V93, P254, DOI 10.1038/labinvest.2012.159, DOI	2013	5.26	2014	2018	
Herold S, 2013, AM J PHYSIOL-LUNG C, V305, PL665, DOI 10.1152/ajplung.00252.2013, DOI	2013	8.13	2015	2018	
Mehta D, 2014, AM J PHYSIOL-LUNG C, V307, PL924, DOI 10.1152/ajplung.00318.2014, DOI	2014	5.32	2015	2019	
Gong HX, 2015, J CLIN INVEST, V125, P652, DOI 10.1172/JCI77701, DOI	2015	6.01	2016	2019	
Bellani G, 2016, JAMA-J AM MED ASSOC, V315, P788, DOI 10.1001/jama.2016.0291, DOI	2016	15.68	2017	2021	
Gill SE, 2015, RESP RES, V16, P0, DOI 10.1186/s12931-015-0266-7, DOI	2015	6.25	2017	2019	
Thompson BT, 2017, NEW ENGL J MED, V377, P562, DOI 10.1056/NEJMra1608077, DOI	2017	10.77	2019	2023	
Fan E, 2018, JAMA-J AM MED ASSOC, V319, P698, DOI 10.1001/jama.2017.21907, DOI	2018	7.57	2019	2023	
Matthay MA, 2019, NAT REV DIS PRIMERS, V5, P0, DOI 10.1038/s41572-019-0069-0, DOI	2019	20.71	2020	2023	
Varga Z, 2020, LANCET, V395, P1417, DOI 10.1016/S0140-6736(20)30937-5, DOI	2020	6.51	2020	2023	
Ackermann M, 2020, NEW ENGL J MED, V383, P120, DOI 10.1056/NEJMoa2015432, DOI	2020	10.19	2021	2023	
Vassiliou AG, 2020, INT J MOL SCI, V21, P0, DOI 10.3390/ijms21228793, DOI	2020	6.32	2021	2023	
Dong WJ, 2018, AUTOPHAGY, V14, P1677, DOI 10.1080/15548627.2018.1476811, DOI	2018	5.27	2021	2023	

Fig. 8. Visual map of references on endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome **(A)**Clustered network diagram of references related to endothelial barrier versus epithelial barrier in acute lung injury and acute respiratory distress syndrome **(B)**Schematic visualization of the reference network **(C)**Top 25 references for the strongest citation explosion.

Table 5
Top 10 most cited references on endothelial barrier and epithelial barrier in acute lung injury and acute respiratory distress syndrome.

Rank	Title	Corresponding Author	Journal (IF 2022)	Publication year	Total citations(n)	Cluster ID
1	Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19	Ackermann M	*New Engl J Med*(IF 158.5)	2020	27	2
2	Novel concepts of acute lung injury and alveolar-capillary barrier dysfunction	Barabutis N	*Am J Physiol-Lung C* (IF 4.9)	2013	19	0
3	Endothelial cell infection and endotheliitis in COVID-19	Varga Z	*Lancet*(IF 168.9)	2020	18	2
4	Wild-type p53 enhances endothelial barrier function by mediating RAC1 signalling and RhoA inhibition	Barabutis N	*J Cell Mol Med* (IF 5.3)	2013	17	9
5	Endothelial Damage in Acute Respiratory Distress Syndrome	Vassiliou AG	*INT J MOL SCI* (IF 5.6)	2020	17	5
6	Regulation and repair of the alveolar-capillary barrier in acute lung injury	Bhattacharya J	*ANNU REV PHYSIOL* (IF 18.2)	2013	13	0
7	HIF2α signaling inhibits adherens junctional disruption in acute lung injury	Gong HX	*J CLIN INVEST* (IF 15.9)	2015	13	0
8	Stimulation of Rho signaling by pathologic mechanical stretch is a "second hit" to Rho-independent lung injury induced by IL-6	Birukova AA	*AM J PHYSIOL-LUNG C* (IF 4.9)	2012	13	10
9	Measurement of local permeability at subcellular level in cell models of agonist- and ventilator-induced lung injury	Dubrovskyi O	*LAB INVEST* (IF 5.0)	2013	13	4
10	Role of pulmonary microvascular endothelial cell apoptosis in murine sepsis-induced lung injury in vivo	Gill SE	*RESP RES* (IF 5.8)	2015	12	0

3.8. Analysis of the current state of research on endothelial/epithelial barriers and COVID-19 in ALI/ARDS

Numerous recent studies have investigated COVID-19-induced ALI/ARDS in the endothelial and epithelial barriers as a consequence of the COVID-19 outbreak. Fig. 2 illustrates that the rapid expansion of NP on the endothelial and epithelial barriers in ALI/ARDS became attributed to COVID-19 since 2020 (Fig. 9). To gain deeper insight into the patterns and advancements of relevant

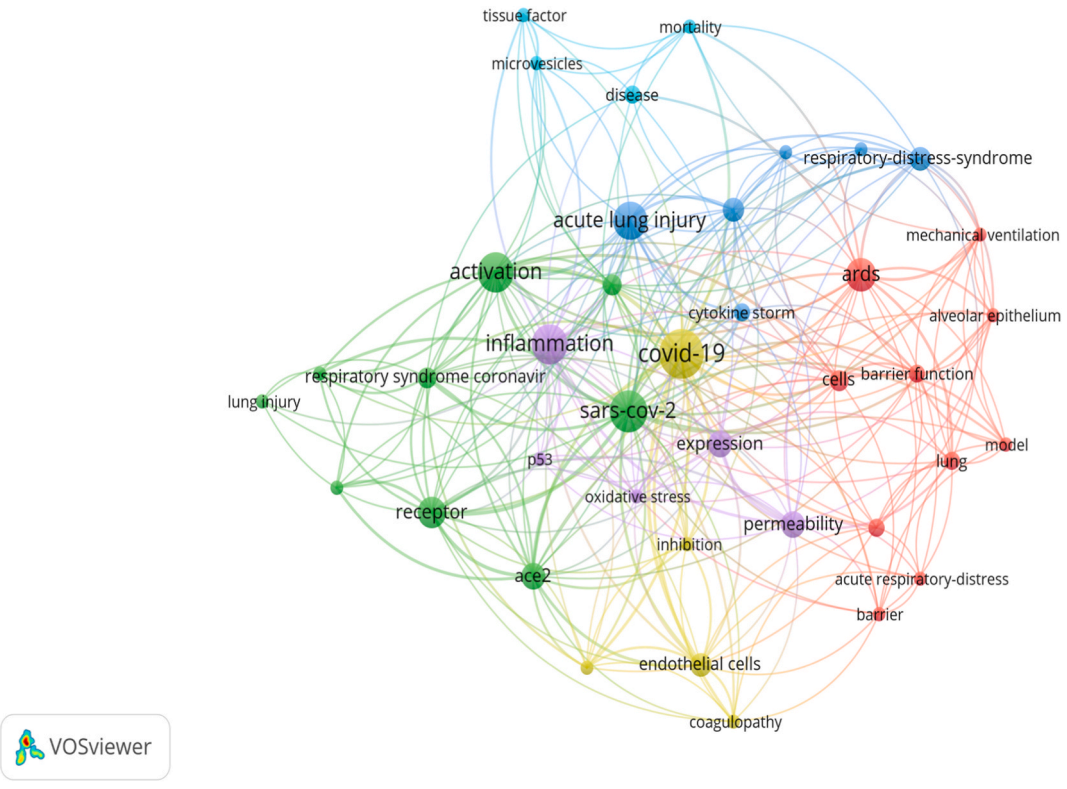

Fig. 9. Keyword co-occurrence graph of COVID-19-induced endothelial barrier and epithelial barrier in ALI/ARDS: a total of 39 keywords appeared more than 3 times and were classified into 6 categories according to color. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

studies in this particular domain, we examined 56 articles associated with COVID-19/SARS-COV-2. Inflammation, receptor activation, and permeability were the most frequent terms, followed by COVID-19/SARS-COV-2-related lung diseases, indicating the involvement of endothelial and epithelial barriers in the development of ALI/ARDS induced by COVID-19.

3.9. Annotation of target genes, pathways, and related protein interactions

To further elucidate the research hotspots of endothelial/epithelial barriers in ALI/ARDS, we extracted 4009 keywords from the literature and 12,564 genes related to endothelial/epithelial barriers in ALI/ARDS from the Gencards database. Subsequently, we imported the data into R (4.2.1) to analyze the unique and shared parts between each group. We extracted a total of 110 related genes, and the results were visualized using the ggplot2 package and the Venn Diagram package (Fig. 10A). Among these 110 genes, we extracted the top 20 related genes in terms of frequency of occurrence, and the top five genes were RHOA, RHO, CAMP, TRPV4, and ACE2 (Fig. 10B–. C, and Fig. 10D). Functional annotation and significant enrichment analysis in GO showed that biological processes were mainly expressed in epithelial cell migration, response to oxygen levels, and regulation of angiogenesis. We also found that cellular components were mainly located in extracellular regions, whereas molecular function was mainly distributed in the binding sites of DNA and transcription factors. The results of further analysis of KEGG pathway enrichment are shown in Fig. 11A. Table 6 details the outcome of GO/KEGG enrichment analysis. The most relevant genes for KEGG pathway enrichment were AKT1 and PI3KR2. KEGG pathway enrichment analysis showed that PI3K-Akt signaling pathway, Rap1 signaling pathway, and Sphingolipid signaling pathway were endothelial/epithelial barriers in ALI/ARDS. Popular research pathways KEGG pathway enrichment analysis showed that PI3K-Akt signaling pathway, Rap1 signaling pathway, and Sphingolipid signaling pathway are endothelial/epithelial barriers in ALI/ARDS (Fig. 11B). The DEGs PPI network was constructed by STRING online database to understand the protein-protein interaction, where a node represents a gene and edges represent interactions between genes. Fig. 11C shows that AKT1, PI3KR2, RHOA, and SRC have significant interactions with other proteins.

4. Discussion

The first study on this subject was published in 2011 by Wolfson et al. [35]. Between 2010 and 2023, the number of publications increased from 28 to 76, and the marked increase in COVID-19 cases may have been responsible for the surge in publications after 2020. The United States is home to eight of the top ten institutions with the highest intermediary centrality. Moreover, the publication counts and overall citations of studies from the United States exceeded those of studies from China. Thus, based on the contributions of countries and institutions, the United States led the field. The annual cumulative number of publications from China in the area plot of annual publications increased significantly, indicating that China occupies an increasingly important position in the study of endothelial and epithelial barriers in ALI/ARDS.

Birukova AA was the most prolific and cited author in the field and had conducted extensive research on the correlation between lung disease and endothelial damage caused by molecular and cytogenetic factors (Table 2). He proposed that iloprost improved the functionality of the endothelial barrier in lipopolysaccharide-triggered lung injury [36]. The strongest link was between Birukova AA and Garcia JGN, who, in their co-authored article, “Shear stress-mediated cytoskeletal remodeling and cortactin translocation in pulmonary endothelial cells,” revealed the potential role of cortical actin in shear stress-induced remodeling of the endothelial cell cortical cytoskeleton and demonstrated a novel mechanism for Rac GTPase-dependent regulation of the pulmonary endothelial cytoskeleton by shear stress [37]. These authors are highly regarded for their extensive explanation of the mechanisms of the endothelial-epithelial barrier and their valuable contributions in preventing ALI/ARDS.

Among the top 10 journals in terms of the number of articles published, most of the JCR divisions are $\geq$ Q2. This suggests that these journals are highly innovative, leading, and have significant impact on the field. *American Journal of Physiology-Lung Cellular and Molecular Physiology* had the highest impact among the top 10 journals in terms of the number of published articles (Table 3). This journal is a scholarly journal published by the American Physiological Society, with the objective to feature innovative studies concerning the cellular and molecular functioning of the respiratory system. Its scope includes investigations of lung physiology, lung ailments, respiratory ailments, lung infections, lung inflammation, and lung immunity. Multidisciplinary journals have a broader audience and facilitate interdisciplinary collaboration among scholars.

Building on the keyword map, inflammation significantly impacts the pathogenesis of the endothelial-epithelial barrier. The alveolar epithelium has several important biological functions. For example, it establishes a natural physical barrier against antigenic substances entering the body and initiates intrinsic immunity by establishing an antiviral state and activating various immune cells [38]. When faced with specific inflammatory triggers, a significant number of immune cells gather at the site of injury, initiating a sequence of signals that promote inflammation and release numerous proinflammatory substances that harm the lung epithelium [39]. Damage to epithelial cells involves the dissociation of intercellular junctions and increased paracellular permeability, a process that involves the dysregulation of tight junction proteins (e.g., occlusion band (ZO) proteins) or adhesion junction proteins (e.g., e-calmodulin) and actin cytoskeletal rearrangement [40]. Pulmonary microvascular endothelial cells play a key role in maintaining the functional integrity of the endothelial barrier [41]. Similar to monolayer epithelial cells, endothelial cells form intercellular junctions, including adherens junctions, tight junctions, and gap junctions, and limit the diffusion of proteins and fluids out of the vascular system [41,42]. Contraction and anchoring forces play significant roles in the regulation of the paracellular barrier in endothelial cells. Additionally, the binding of microfilament proteins, level of myocardin light chain phosphorylation, and number of intercellular junctions determine the contraction and integrity of endothelial cells, thereby affecting barrier function/dysfunction [43]. Inflammatory mediators, including vasoactive amines, bradykinins, and reactive oxygen metabolites, activate various intracellular signaling

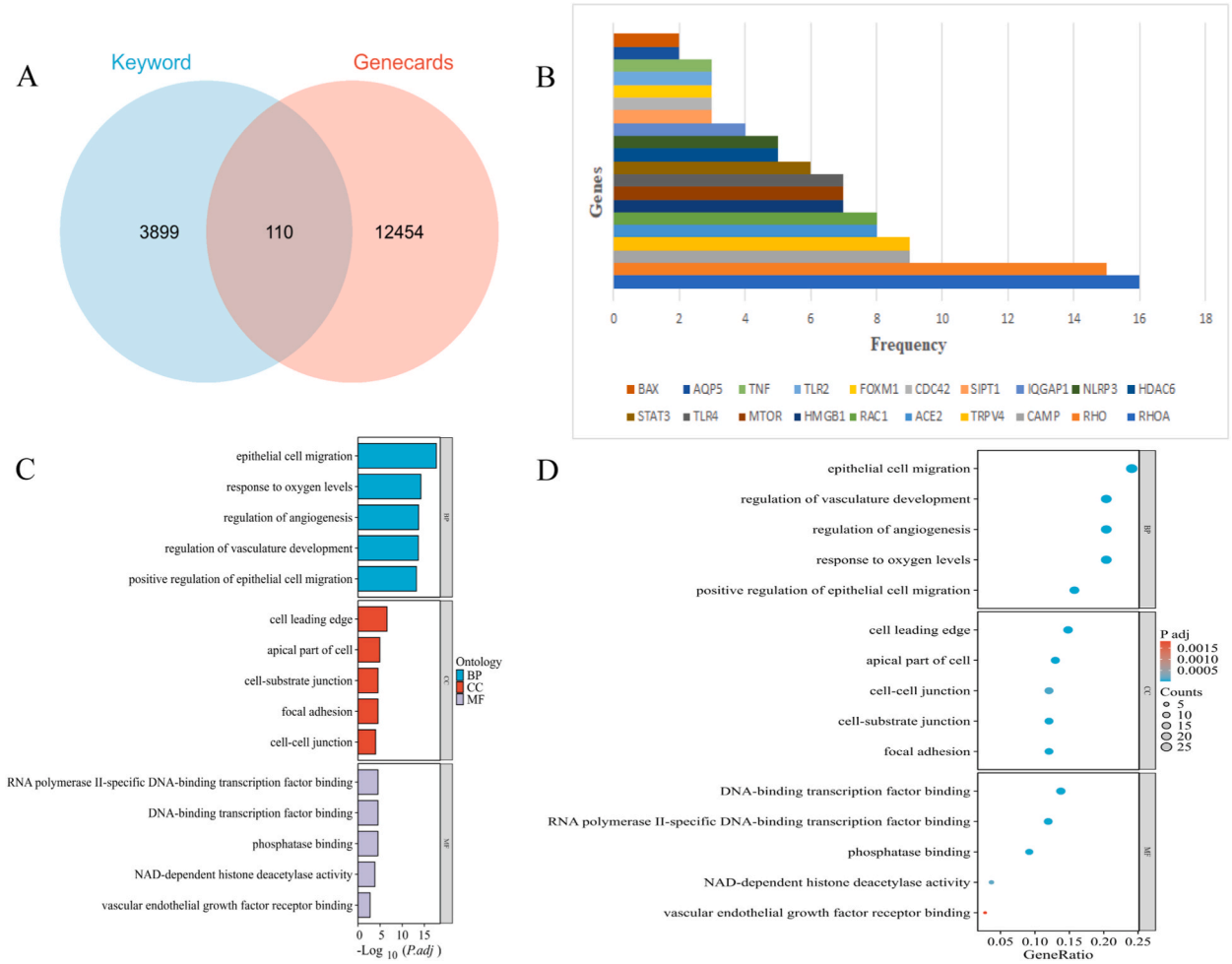

Fig. 10. Annotated target genes and pathways on endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome (A) 110 keyword genes in a Wayne diagram (B) The 20 high-frequency genes (C) Bar graph of the results of GO functional annotation and enrichment analysis of literature gene keywords (D) Bubble plots of GO functional annotation and enrichment analysis results for literature gene keywords.

pathways by binding to specific receptors on the surface of the endothelial cell. Activation of these inflammatory pathways creates gaps between cells, ultimately increasing the permeability of fluids and macromolecules across the endothelial layer [44]. Research has also demonstrated that the regulation of pulmonary endothelial and alveolar epithelial barriers is achieved through distinct actin remodeling and cytoskeletal interactions with tight junction complexes [45,46].

Regarding the effect of the endothelial-epithelial barrier on ALI and ARDS, COVID-19 is significantly associated with endothelial-epithelial barrier-mediated lung disease (Fig. 9A). The COVID-19 virus is extremely infectious and causes severe complications, particularly ARDS [47–49]. A pathological study of the postmortem lungs of patients with COVID-19 showed that mild viral infections have a limited effect on the upper respiratory tract and a negligible effect on lung tissue integrity. However, severe viral infections can lead to diffuse alveolar damage, which is characterized by apoptosis, necrosis, detachment of alveolar epithelial cells, and infiltration of inflammatory cells in the alveolar lumen, ultimately leading to hypoxemia, fibrosis of lung tissues, and death [50]. Individuals affected by COVID-19 display endothelial cell involvement in different vascular networks of organs, accompanied by the presence of viral elements within these cells, ultimately leading to the death of endothelial and immune cells [51]. This also causes loss of the integrity of the epithelial-endothelial (air-blood) barrier and exudates in the alveolar lumen. This mechanism aligns with imaging observations that indicate signs of interstitial alveolar injury, such as B-lines, lungs with ultra-white patches, patchy areas resembling hairy-glass cloudy, hazy regions, and a slight increase in density on CT scans [51,52]. SARS-CoV-2 can trigger systemic inflammatory response syndrome, which causes the release of excessive inflammatory mediators and a 'cytokine storm', which has the potential to induce pulmonary vascular endothelial inflammation, thrombosis, vasodilation, and overperfusion of collapsed lung tissue [29,53]. Therefore, exploring therapeutic targets linked to lung epithelial and endothelial damage holds immense promise in the treatment of COVID-19 and in mitigating related illnesses and deaths.

When annotating genes and related pathways, RhoA appeared most frequently among gene-related keywords, and the PI3K-AKT signaling pathway had the highest number of KEGG pathway enrichments. Rho family proteins are considered the main regulatory

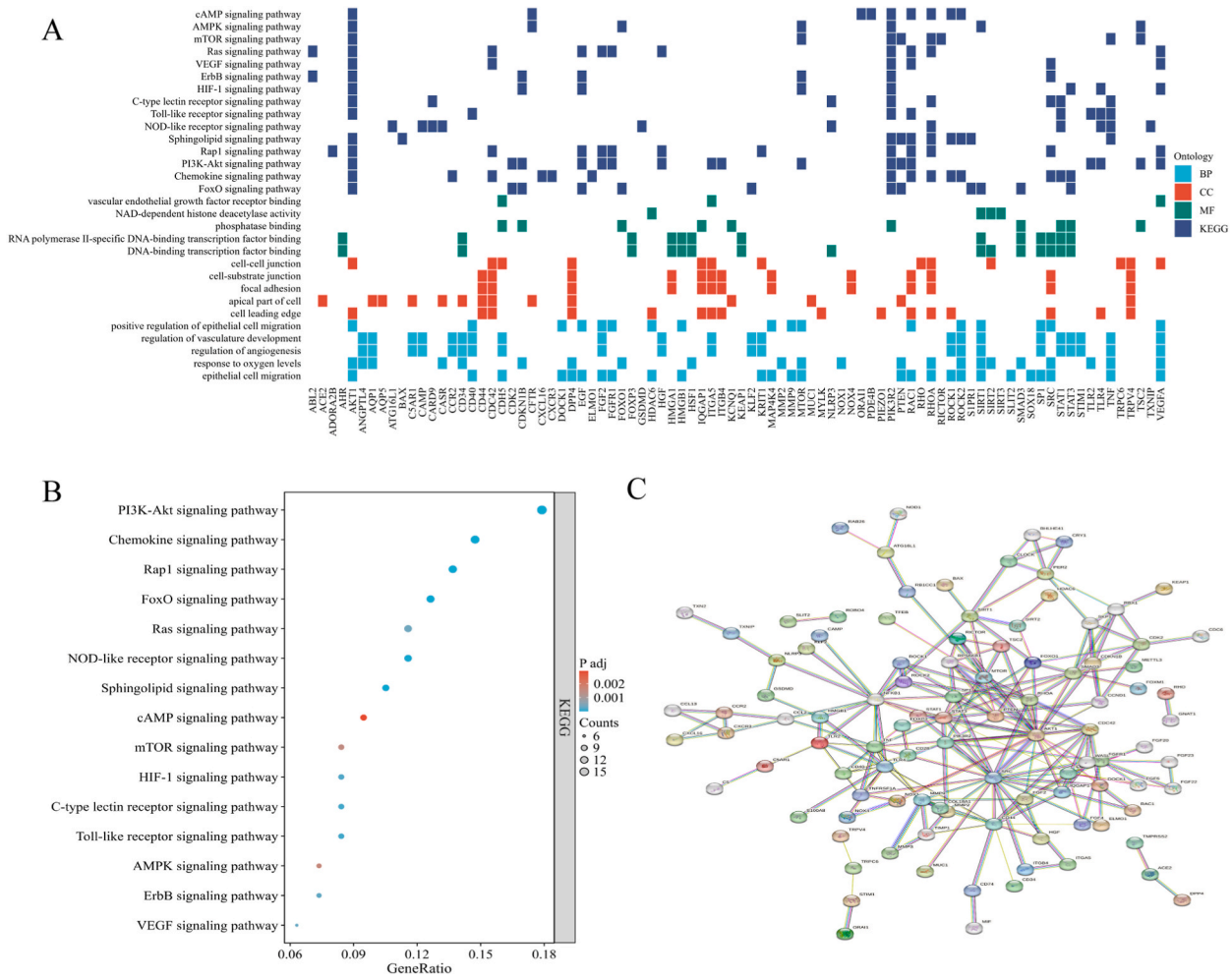

Fig. 11. Target Gene and Pathway Annotation and PPI on endothelial and epithelial barriers in acute lung injury and acute respiratory distress syndrome **(A)** GO/KEGG Heat Map of 110 literature gene keywords **(B)** Results of KEGG pathway enrichment analysis of 110 literature gene keywords **(C)** PPI network of 110 keyword genes.

molecules governing endothelial barrier function by regulating endothelial permeability, which causes the flow of protein-rich fluids to the interstitium, as well as the migration of neutrophils and infiltration of inflammatory cytokines, which is a common feature of many injury syndromes, including ARDS [54,55]. The negative role of Rho in endothelial barrier function has long been recognized, and the signaling pathway of RhoA often contributes to the mechanisms leading to increased permeability [56]. RhoA can destabilize endothelial barrier properties by promoting myocardin light chain-dependent contraction of stress fibers and reducing VE-calmodulin-mediated adhesion via Rho kinase[54]. In a previous study, it was shown that the PI3K-AKT signaling pathway mediates the formation of intercellular junctions associated with barrier dysfunction, changes in cell migration, and cell proliferation [57]. It is important to note that inflammation and endothelial permeability are interrelated pathological events, and previous studies have shown that LPS has a dual effect on endothelial cell barrier function through the PI3K-AKT signaling pathway, with low doses inducing hyperpermeability of the pulmonary microvasculature through the AT1 receptor and high doses having the opposite effect [58,59]. Considering the critical role of RhoA and PI3K-AKT signaling pathways in the endothelial barrier, inhibition of RhoA or PI3K-AKT signaling pathways may serve as a potential therapeutic target for the treatment of ALI/ARDS. Some drugs, such as sevoflurane and oxidized berberine, have been found to reduce alveolar epithelial barrier damage and permeability via RhoA in experimental models, ultimately preventing ALI progression [40,60].

We conducted a visual analysis of scientific research on endothelial and epithelial barriers in ALI/ARDS to explore the current state of research in this field from 2010 to 2023. However, this study had some limitations. (1) This study solely incorporated articles and reviews from Science Citation Index Expanded in English, potentially excluding articles in different languages and other article types. (2) Owing to the challenge of merging the two datasets for analysis, this study relied solely on the WoSCC database to search for pertinent publications, while overlooking publications in PubMed, Embase, Scope, and other databases. Consequently, this approach might have introduced a selection bias. (3) Because the database is updated quickly, some of the latest studies on the subject may not

Table 6
GO/KEGG enrichment analysis on endothelial barrier and epithelial barrier in acute lung injury and acute respiratory distress syndrome.

Ontology	ID	Description	Gene Ratio	Bg Ratio	*p* value	*p*.adjust
BP	GO:0010631	epithelial cell migration	26/108	358/18800	1.27e-21	1.92e-18
BP	GO:0070482	response to oxygen levels	22/108	324/18800	9.92e-18	6.09e-15
BP	GO:0045765	regulation of angiogenesis	22/108	345/18800	3.77e-17	1.94e-14
BP	GO:1901342	regulation of vasculature development	22/108	351/18800	5.42e-17	2.22e-14
BP	GO:0010634	positive regulation of epithelial cell migration	17/108	174/18800	1.61e-16	5.93e-14
CC	GO:0031252	cell leading edge	16/108	416/19594	1.09e-09	2.86e-07
CC	GO:0045177	apical part of cell	14/108	424/19594	8.76e-08	1.14e-05
CC	GO:0005925	focal adhesion	13/108	419/19594	5.31e-07	2.94e-05
CC	GO:0030055	cell-substrate junction	13/108	428/19594	6.75e-07	2.94e-05
CC	GO:0005911	cell-cell junction	13/108	497/19594	3.53e-06	0.0001
MF	GO:0140297	DNA-binding transcription factor binding	15/109	470/18410	1.15e-07	2.98e-05
MF	GO:0061629	RNA polymerase II-specific DNA-binding transcription factor binding	13/109	348/18410	1.44e-07	2.98e-05
MF	GO:0019902	phosphatase binding	10/109	193/18410	2.2e-07	3.04e-05
MF	GO:0017136	NAD-dependent histone deacetylase activity	4/109	15/18410	1.51e-06	0.0002
MF	GO:0005172	vascular endothelial growth factor receptor binding	3/109	14/18410	7.01e-05	0.0018
KEGG	hsa04068	FoxO signaling pathway	12/95	131/8164	3.09e-08	5.41e-07
KEGG	hsa04062	Chemokine signaling pathway	14/95	192/8164	3.79e-08	6.13e-07
KEGG	hsa04151	PI3K-Akt signaling pathway	17/95	354/8164	5.36e-07	6.25e-06
KEGG	hsa04015	Rap1 signaling pathway	13/95	210/8164	8.1e-07	8.95e-06
KEGG	hsa04071	Sphingolipid signaling pathway	10/95	119/8164	1.05e-06	1.11e-05
KEGG	hsa04621	NOD-like receptor signaling pathway	11/95	184/8164	8.51e-06	5.58e-05
KEGG	hsa04620	Toll-like receptor signaling pathway	8/95	104/8164	2.57e-05	0.0001
KEGG	hsa04625	C-type lectin receptor signaling pathway	8/95	104/8164	2.57e-05	0.0001
KEGG	hsa04066	HIF-1 signaling pathway	8/95	109/8164	3.62e-05	0.0002
KEGG	hsa04012	ErbB signaling pathway	7/95	85/8164	5.45e-05	0.0003
KEGG	hsa04370	VEGF signaling pathway	6/95	59/8164	5.81e-05	0.0003
KEGG	hsa04014	Ras signaling pathway	11/95	235/8164	8.24e-05	0.0004
KEGG	hsa04150	mTOR signaling pathway	8/95	156/8164	0.0004	0.0015
KEGG	hsa04152	AMPK signaling pathway	7/95	121/8164	0.0005	0.0016
KEGG	hsa04024	cAMP signaling pathway	9/95	221/8164	0.0010	0.0029

have been included. However, employing this visual method to comprehend the present condition, focal points, and patterns of investigation in a specific domain is valuable because it can help scholars enhance their understanding of the pertinent domain and expedite further research.

5. Conclusion

This bibliometric analyses revealed that promising research has been conducted on endothelial and epithelial barriers in ALI and ARDS. The major contributors, countries, journals, and institutions in the field were identified. In the domain, both the United States and China have been major contributors, with inflammation having a notable effect on the development of ALI and ARDS in the endothelial and epithelial barriers. RHOA appeared most frequently among gene-related keywords, and the PI3K-AKT signaling pathway had the highest count in KEGG pathway enrichment. Given the high incidence of COVID-19, there may be a new research direction in this area focusing on identifying novel therapeutic targets to mitigate endothelial and epithelial barrier dysfunction, which can delay the advancement of COVID-19-related lung disease.

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Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

CRediT authorship contribution statement

Zixin Luo: Writing – original draft, Validation, Supervision, Software, Resources, Formal analysis, Data curation. **Xinyue Song:** Writing – review & editing, Project administration, Methodology. **Duoqin Huang:** Writing – original draft, Validation, Supervision, Software, Resources. **Li Xiao:** Writing – original draft, Visualization, Project administration, Conceptualization. **Kang Zou:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Kang Zou reports financial support was provided by the Guidance Science and Technology Plan Project, Ganzhou Science and Technology Bureau, China (GZ2018ZSF074). Kang Zou reports financial support was provided by Science and Technology and Healthcare Joint Program Project, Ganzhou Science and Technology Bureau, China (2023LNS36644). Kang Zou reports financial support was provided by Science and Technology Program, Jiangxi Provincial Health Commission, China (202410348). None If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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