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Research trends and hotspots on global influenza and inflammatory response based on bibliometrics

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Abstract

The influenza virus is considered as a kind of significant zoonotic infectious disease identified to date, with severe infections in humans characterized by excessive inflammation and tissue damage, usually resulting in serious complications. Although the molecular mechanisms underlying inflammation after influenza infection have been extensively studied, bibliometric analysis on the research hotspots and developing trends in this field has not been published heretofore. Articles related to influenza and inflammatory response were retrieved from the Web of Science Core Collection (WoSCC) database (1992–2024) and analyzed using various visualization tools. Finally, this study collected a total of 2,176 relevant articles, involving 13,184 researchers, 2,647 institutions, 78 countries/regions, and published in 723 journals. Most articles were published in the United States (928 articles), China (450 articles) and the United Kingdom (158 articles). Ross Vlahos was the most productive author. Furthermore, some journals, such as PLoS One and Frontiers in Immunology, made much contribution to the topic. The future research trends include airway stem cells and neuroendocrine cells as new directions for the treatment of influenza complications, as well as measures related to prevention, treatment, and research and development based on the COVID-19 pandemic. Through bibliometric analysis and summary of inflammatory response of influenza-related articles, this study ultimately summarizes new directions for preventing and treating influenza.

Keywords Influenza, Inflammatory response, Bibliometric analysis, Developing trends, Visualization tools

Introduction

Influenza virus has caused four global pandemics in humans since 1918 owing to the emergence of new variants [1]. Notably, only influenza A virus (IAV) is able to infect a variety of species, such as humans, pigs, horses, and birds, with high transmissibility, leading to global pandemics. Besides, IAV is one of the most common viruses in clinical practice [2, 3]. The infection typically begins in the upper respiratory tract and invades the cells through the epithelial mucous layer, inducing host innate immune responses. Consequently, an array of immune effector cells, such as neutrophils and macrophages, are summoned by the infected airway epithelial cells, which

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results in heightened inflammation and damage to local tissues [4–6].

Epithelial cells are initiators and builders of host responses in the lung. Influenza infection can upregulate bacterial adhesion receptors, promoting bacterial colonization and invasion [7, 8]. Upon influenza infection, alveolar epithelial cells activate a series of pattern recognition receptors, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I like receptors (RLRs), leading to a robust inflammatory response within the lungs [9, 10].

Proteins, such as polymerase basic protein 1 (PB1), nucleoprotein (NP), matrix protein 2 (M2), nonstructural protein 1 (NS1) are encoded by the IAV genome. These proteins play important roles in host inflammatory responses [11–13]. The matrix protein 1 (M1) of IAV specifically binds to cysteine proteases, leading to inflammatory necrotic apoptosis in cells [14]. Both host and viral factors can promote epithelial inflammation in influenza-infected cells, leading to secondary bacterial infections [15, 16]. Therefore, antiviral epithelial responses are crucial for regulating lung inflammation and influenza-related bacterial diseases. However, no comprehensive bibliometric study has been undertaken to examine the current trends and status of research on influenza-induced inflammatory responses.

Bibliometrics involves quantitative analysis from different fields, such as mathematics and statistics. Bibliometrics was founded in 1969. Besides library science, publications, institutions, authors, and countries/regions can be statistically analyzed and visualized to understand the current tendency and condition of a research field [17]. Herein, bibliometrics was applied to explore the trends in the study of influenza over the past thirty years and predict future research trends for establishing mapping knowledge domains.

Methods

Data and retrieval strategy

The articles related to influenza inflammatory response were retrieved from the Web of Science Core Collection (WoSCC) data base. The correlative data prior to April 8, 2024, were downloaded to ensure that all the data were consistently searched. The following key search terms were used: TS= (("Influenza" OR "Flu") AND ("Inflammatory Reaction" OR "Inflammation")), covering the period from January 1, 1992, to April 8, 2024. A total of 13,606 articles were obtained. The articles were filtered by two individuals based on the inclusion and exclusion criteria (Fig. 1). Finally, 2,176 valid publications were obtained. The articles were subsequently saved in a plain text format for subsequent scrutiny.

Bibliometrics and visualization analysis

The development overview, trends, and new frontier hotspots of influenza inflammatory response research over the past three decades, including distribution by institutions, journals, countries/regions, and keywords, were analyzed using various softwares, such as VOSviewer [version 1.6.18], Scimago Graphica [version 1.0.42] and CiteSpace [version 6.1], and website https://bibliometric.com/application.

CiteSpace [Version 6.1] is widely used to visualize scientific literature analysis, citation counts, total publications, key disciplines and journals, research institutions and collaboration, and author analysis [18]. This software can also perform clustering and burst analysis, such as analyzing keyword frequency and keyword clustering. In the co-occurrence analysis map, node size represents publication counts, the interconnections between nodes symbolize cooperation, and the thickness of a link reflects the frequency of collaboration. The co-presence or co-citation relationship is more active when more nodes are interconnected, and the connections are thicker [19]. The knowledge system of a certain area can be presented based on cited references, where the highly referred one is usually recognized as classic and authoritative in a research field. The nodes in the network represent citations, and their sizes are proportional to their co-citation frequencies. Connections between nodes indicate co-citation in the literature. In summary, CiteSpace [Version 6.1] can visualize the networks of main authors and institutions in specific research areas.

VOSviewer [version 1.6.18] is widely used for analyzing and visualizing scientific literature, keywords, author relationships and so on. This software can also be used for co-occurrence analysis, network visualization, heat maps, cluster analysis, etc [20]. In the generated co-citation map, node represents each element (scientific literature, keywords, authors, etc.); nodes of the same color indicate a certain degree of association; the diameter of a node represents the number of articles or citations related to it; larger nodes indicate key research topics in the field. The distance between two nodes represents the relationship between the two elements, with shorter distances indicating stronger relationships and vice versa [21]. The geographic distribution of research on inflammation in influenza was created using Scimago Graphica [version 1.0.42] and VOSviewer [version 1.6.18]. Scimago Graphica [version 1.0.42] is a network-based tool for creating and editing scientific charts. Besides, to gauge the extent of publications, Microsoft Office Excel 2021 was employed.

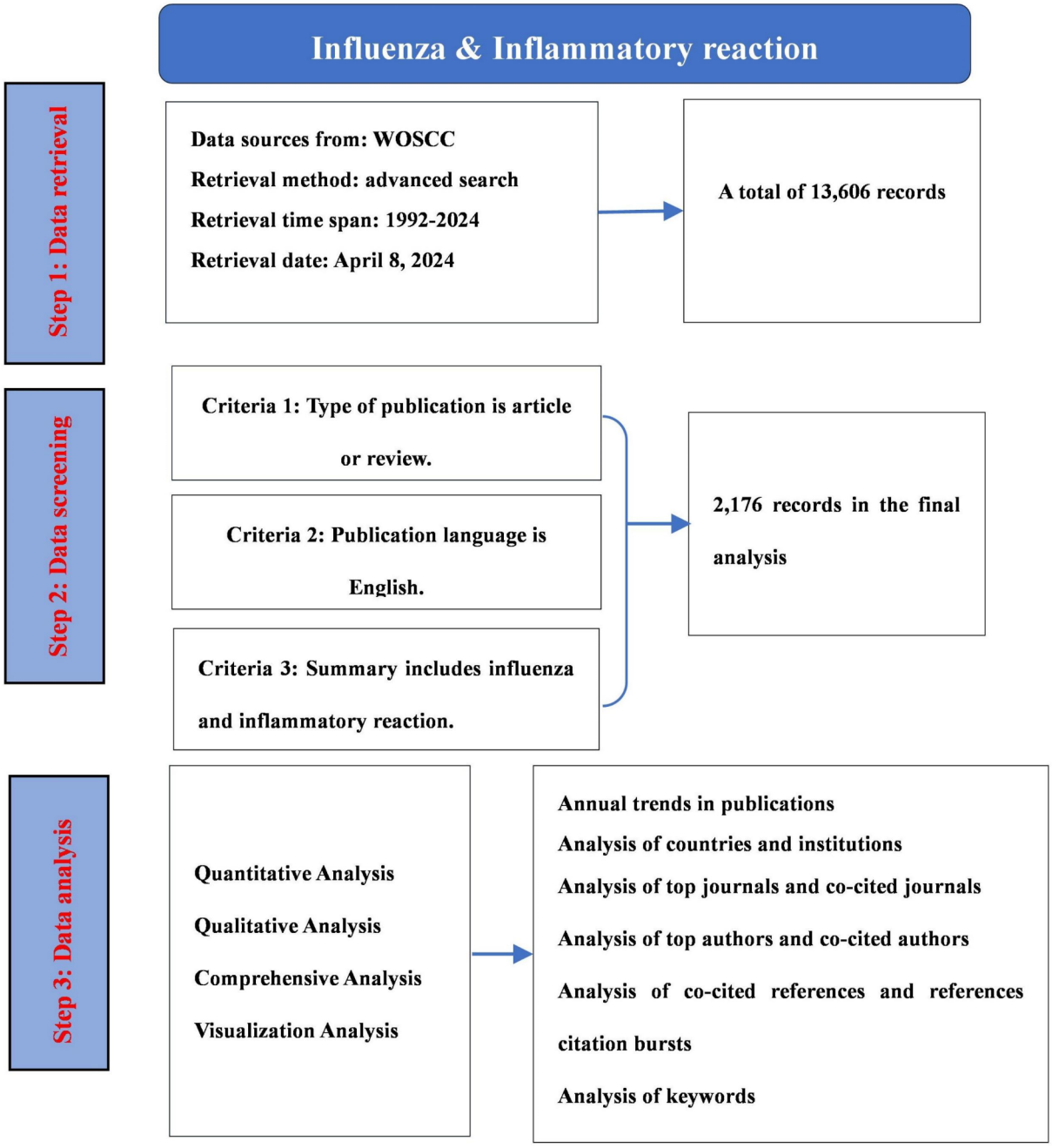


Fig. 1 Flowchart showing the inclusion and exclusion criteria

Results

Chronological trends in publications

The 2,176 articles were published in 723 journals, written by 13,184 researchers from 2,647 institutions in 78 countries/regions. The publishing trends in the past 30 years are shown in Fig. 2. The publications significantly increased after 2009 and 2018, possibly due to the 2009 H1N1pdm09 influenza virus pandemic and the 2019 novel coronavirus pandemic. Publications have been steadily augmenting, with over 110 publications per year since 2015, peaking at 243 publications in 2021, followed by a slight decline, probably the reason the end of the global COVID-19 pandemic. Additionally, the polynomial curve graph revealed that the number of yearly publications increased with time (R^2=0.8707). R^2 is a statistic in polynomial curve regression that helps us understand the degree of fit and predictive ability of the model. These findings indicate that influenza inflammatory response

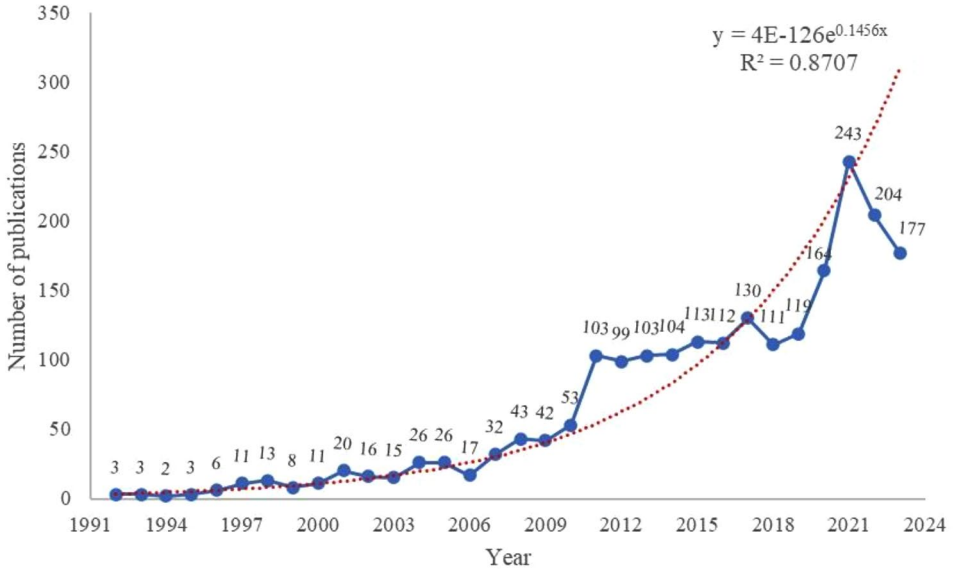


Fig. 2 Worldwide publication growth trends from 1992 to 2024

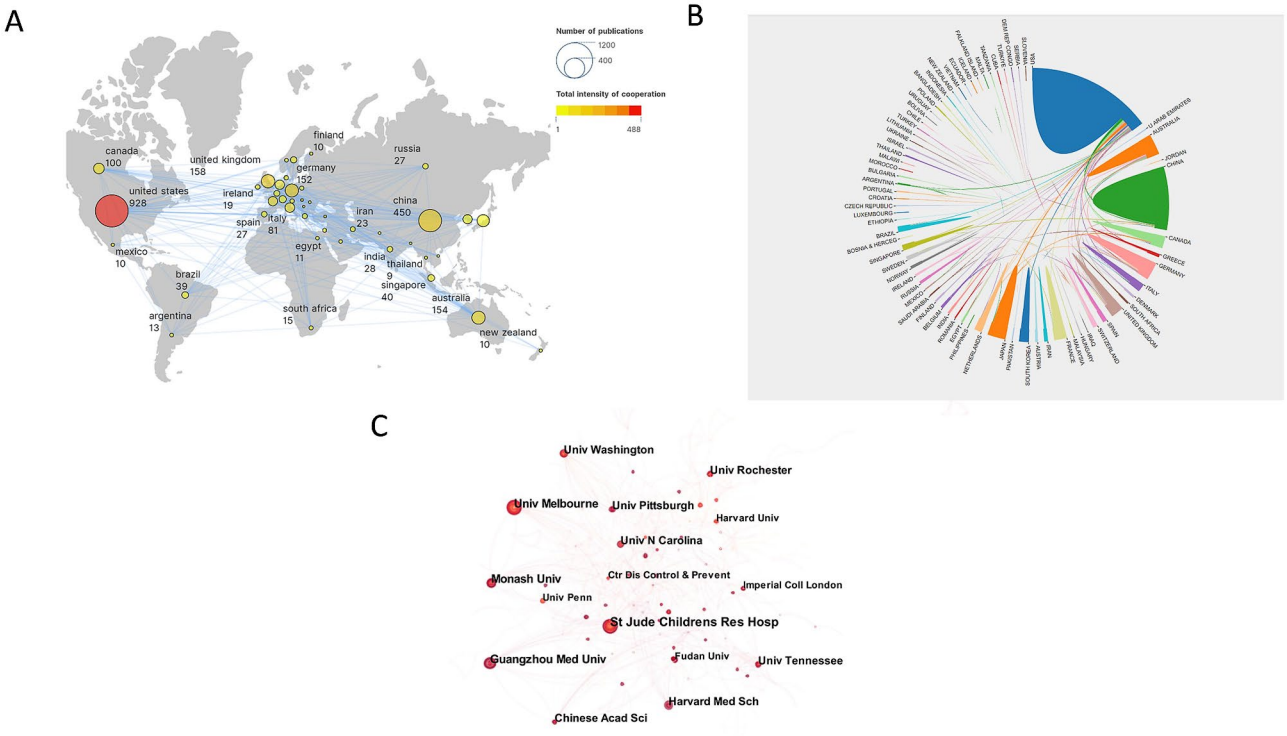


Fig. 3 (**A**). Map showing the geographical spread of publications by country/region on the basis of the total volume of publications and collaborations. (**B**). Map showing publishing cooperation between countries/regions. (**C**). Publishing institutions

has gradually become a hotspot in recent years, especially in influenza study.

Analysis of countries/ regions and institutions

Nearly 100 countries or regions has participated in the study of inflammatory responses in influenza. The spread of these countries/regions and the volume of publications and collaborations are visualized in Fig. 3A. The publication output of the top 10 countries/regions and institutions is listed in Table 1. Most articles were published in the United States (928 articles), China (450 articles), the United Kingdom (158 articles), Australia (154 articles), and Germany (152 articles). Half of the countries/regions by publication output in top 10 are located in Europe,

Table 1 Top 10 countries/regions and institutions in terms of publication volume

Rank	Country	Records	Institutions	Records
1	United States	928	St. Jude Children's Research Hospital	52
2	China	450	University of Melbourne	50
3	United Kingdom	158	Monash University	41
4	Australia	154	Guangzhou Medical University	39
5	Germany	152	University of Washington	39
6	Japan	130	University of North Carolina	34
7	Canada	100	University of Pittsburgh	31
8	Italy	81	University of Rochester	31
9	Netherlands	79	Chinese Academy of Science	29
10	France	76	University of Tennessee	29

with the rest spread across North America, Asia, and Oceania.

Furthermore, some countries/regions formed tight collaborations. The number of articles and the level of cooperation between countries/regions are displayed in Fig. 3B. The United States had the highest number of articles and research partners involving multiple countries/regions, including China and Canada. In addition, China, Australia, and Canada established extensive cooperation with other countries/regions.

Figure 3C. The publishing institutions. St. Jude Children's Research Hospital published the most related literature (52 articles). Besides, most institutions in top 10 are located in the United States, China, Australia.

Analysis of top ranked journals and co-cited journals

723 journals in all have published related research on inflammatory responses related to influenza. PLoS One boasted the highest number of publications (95 articles), secondly Frontiers in Immunology (93 articles), then Journal of Virology (65 articles). The 2,176 articles were cited by 9,479 different journals. The visualization of citations is shown in Fig. 4. In addition, Table 2 lists the top 10 co-cited journals. According to the results, Journal of Immunology ranked number one with 1,250 citations, followed by the Proceedings of the National Academy of Sciences of the United States of America (1,129 citations) and the Journal of Virology (1,119 citations). PLoS One and Nature also appeared in the top ten, with 1,089 citations and 1,035 citations, respectively. Notably, six journals (2024) had an IF score of 10 or higher, with New England Journal of Medicine taking the top spot at 158.5.

Analysis of top authors and co-cited authors

13,184 researchers altogether have assessed the mechanisms of inflammatory responses underlying influenza in the past 30 years. The network of cooperation among researchers is shown in Fig. 5A. Many researchers worldwide have only collaborated with a few other researchers, where collaborations are mostly concentrated within the same country/region. Table 3 presents the top 10 productive authors based on publication count. Professor Ross Vlahos from the School of Health and Biomedical Sciences at RMIT University ranked first with 22 articles. The team led by Ross Vlahos has outstanding research experience in the relationship between smoking and lung diseases (chronic obstructive pulmonary disease) and lung inflammation. They have extensively researched the pathology, drug treatment, signal pathways, and other aspects of related pulmonary disorders like asthma, emphysema, and chronic obstructive pulmonary disease. They have also conducted relevant research on the mechanisms of lung inflammation response and potential prevention or treatment targets [22–25].

Professor Jonathan A. McCullers from the University of Tennessee Health Sciences Center ranked second(19 articles). The professor mainly focuses on the connection between influenza and pneumonia, as well as relevant pathogenesis and therapeutic strategies [26–29]. Michelle D. Tate also published 19 articles. Zifeng Yang (18 articles) and Jie Sun (16 articles) ranked 4th and 5th, respectively. The top 5 authors are from the United States, Australia, China.

Table 3 shows the top 10 co-cited authors and their frequency. Tate MD ranked first (251 times), followed by de Jong MD (194 times), McCullers JA (190 times), Taubenberger JK (168 times), and Tumpey TM (154 times). Figure 5B. The co-citation relationship among authors. Figure 5C. Density plot showing the influence of the co-cited authors.

Analysis of co-cited references and references citation bursts

Co-cited reference is defined as when an article is cited by two or more publications, revealing the importance of the article in a certain area. Herein, the article titled "Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia" published in Nature Medicine by de Jong MD et al. in 2006, was the number one with 159 citations (Fig. 6A). This research suggested that the pathogenesis of H5N1 influenza is primarily linked to high viral load and the resultant intense inflammatory response. Therefore, to optimize clinical management, early diagnosis and potent antiviral therapy should be prioritized to mitigate the exaggerated cytokine response [30]. The detailed information on the top 10 co-cited publications and respective citation counts

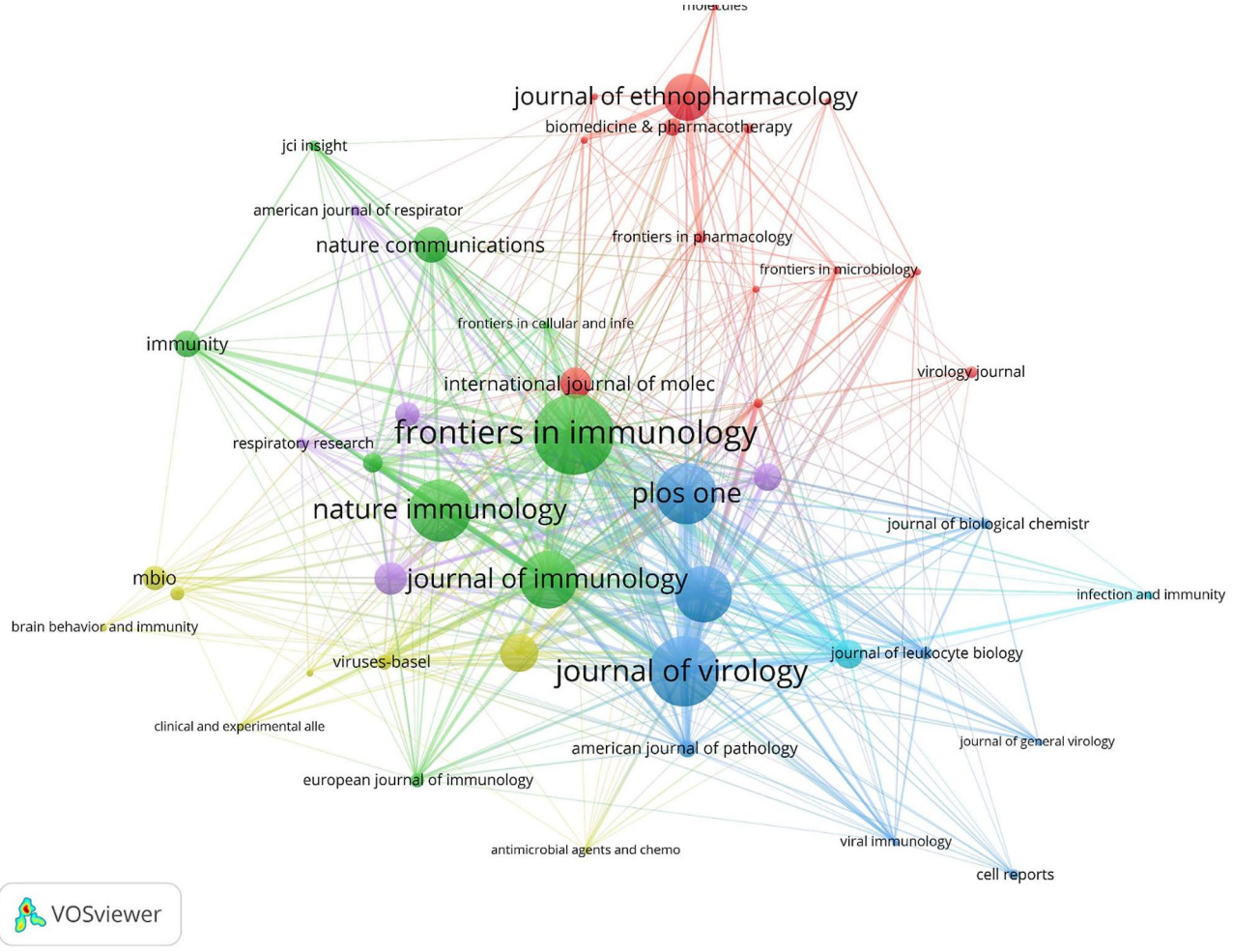


Fig. 4 Visualization of publications on influenza-related inflammatory responses in journals

Table 2 Top 10 journals related to influenza inflammatory response research and co-cited journals

Rank	Journals	Counts	IF (2024)	Co-Cited Journals	Counts	IF (2024)
1	PLoS One	95	3.7	Journal of Immunology	1250	4.4
2	Frontiers in Immunology	93	7.3	Proceedings of the National Academy of Sciences of the United States of America	1129	11.1
3	Journal of Virology	65	5.4	Journal of virology	1119	5.4
4	Journal of Immunology	64	4.4	PloS One	1089	3.7
5	PLoS Pathogens	47	6.7	Nature	1035	64.8
6	Journal of Ethnopharmacology	42	5.4	Science	862	56.9
7	Scientific Reports	32	4.6	Journal of Experimental Medicine	844	15.3
8	American Journal of Physiology-Lung Cellular and Molecular Physiology	31	4.9	New England Journal of Medicine	822	158.5
9	Journal of Infectious Diseases	30	6.4	Journal of Infectious Diseases	821	6.4
10	Viruses-Basel	26	4.7	Journal of Clinical Investigation	769	15.9

are displayed in Fig. 6A. The co-cited articles (over 50 times) and the network graph are shown in Fig. 6B.

References burst analysis detects high-frequency and rapidly growing burst references by examining the temporal distribution of references, then analyzes the frontier areas and development trends of a discipline. Herein, the 15 highest citation bursts according to burst strength are displayed in Fig. 6C. The first references burst occurred in 2006 and the latest one took place in 2020. The longest duration lasts for seven years. The paper was researched

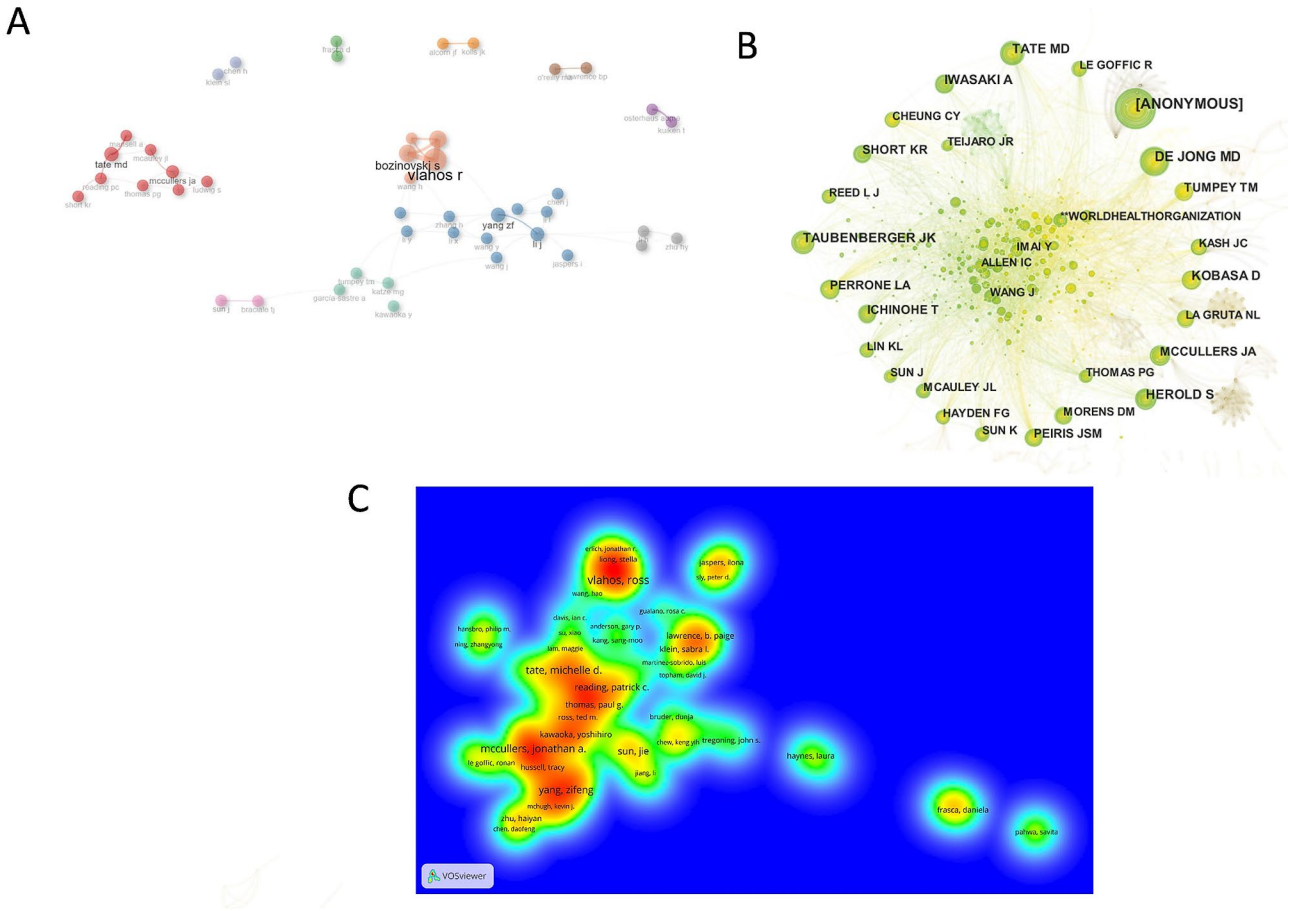


Fig. 5 (**A**). The collaboration among authors. (**B**). Co-Cited authors. (**C**). Co-cited author density chart

Table 3 Top 10 productive authors and co-cited authors

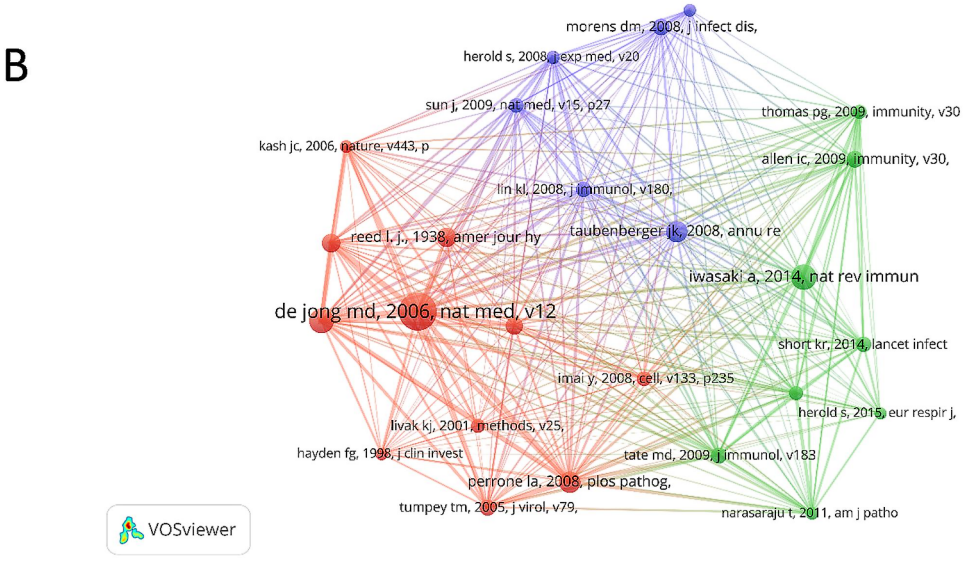
Rank	Authors	Counts	Co-Cited Authors	Citations
1	Ross Vlahos	22	Tate MD	251
2	Jonathan A McCullers	19	de Jong MD	194
3	Michelle D. Tate	19	McCullers JA	190
4	Zifeng Yang	18	Taubenberger JK	168
5	Jie Sun	16	Tumpey TM	154
6	John F. Alcorn	15	Iwasaki A	152
7	Steven Bozinovski	15	Herold S	143
8	Stavros Selemidis	15	Ichinohe T	137
9	Jing Li	14	Frasca D	135
10	Patrick C Reading	14	Hartshorn KL	135

by Chaolin Huang et al. from the Wuhan Jinyintan Hospital in China, named "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China", published in The Lancet in 2020. This paper presented an analysis of the epidemiological, clinical, laboratory, and radiological features of patients diagnosed with the novel coronavirus. Furthermore, it also reported the therapeutic interventions employed and their impact on patient outcomes [31]. This paper is still in the citation burst stage to date.

Analysis of keywords

Keywords elaborate and summarize an article in a condensed and concise way. One can acquire a comprehensive comprehension of the research landscape, prevalent subjects, and emerging trends in future studies of inflammation reactions in influenza through keyword analysis. Figure 7A is a keyword co-occurrence network graph. Both influenza A virus and the novel coronavirus epidemic have simultaneously occurred in recent years. As a result, researchers have been trying to find similarities between the two diseases for effective response measures. The top 10 most frequent keywords are shown in Table 4. Notably, "infection", "inflammation" and "influenza" appeared 405, 396, and 337 times, respectively, indicating that infection, inflammation and influenza are topics that are highly related. The three keywords, especially infection, have shown a significant upward trend since 2012, indicating that they have been research hot topics in recent years (Fig. 7B).

Key term clustering can help to understand the relationships between such terms, discover hidden structures, and identify similarities and differences. In this study, a clustering map was developed after clustering



C

Top 15 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1992 - 2024
Kobasa D, 2007, NATURE, V445, P319, DOI 10.1038/nature05495, DOI	2007	14	2007	2013	
de Jong MD, 2006, NAT MED, V12, P1203, DOI 10.1038/nm1477, DOI	2006	11.44	2008	2011	
La Gruta NL, 2007, IMMUNOL CELL BIOL, V85, P85, DOI 10.1038/sj.icb.7100026, DOI	2007	10.27	2008	2013	
Perrone LA, 2008, PLOS PATHOG, V4, P0, DOI 10.1371/journal.ppat.1000115, DOI	2008	11.52	2010	2013	
Taubenberger JK, 2008, ANNU REV PATHOL-MECH, V3, P499, DOI 10.1146/annurev.pathmechdis.3.121806.154316, DOI	2008	9.49	2010	2013	
Tate MD, 2009, J IMMUNOL, V183, P7441, DOI 10.4049/jimmunol.0902497, DOI	2009	8.73	2010	2015	
Itoh Y, 2009, NATURE, V460, P1021, DOI 10.1038/nature08260, DOI	2009	8.51	2010	2015	
Iwasaki A, 2014, NAT REV IMMUNOL, V14, P315, DOI 10.1038/nri3665, DOI	2014	19.36	2014	2019	
Brandes M, 2013, CELL, V154, P197, DOI 10.1016/j.cell.2013.06.013, DOI	2013	10.57	2014	2019	
Gao RB, 2013, NEW ENGL J MED, V368, P1888, DOI 10.1056/NEJMoa1304459, DOI	2013	10.41	2014	2017	
Liu Q, 2016, CELL MOL IMMUNOL, V13, P3, DOI 10.1038/cmi.2015.74, DOI	2016	8.5	2016	2021	
Iuliano AD, 2018, LANCET, V391, P1285, DOI 10.1016/S0140-6736(17)33293-2, DOI	2018	10.96	2018	2024	
Huang CL, 2020, LANCET, V395, P497	2020	10.61	2020	2024	
Kalil AC, 2019, CRIT CARE, V23, P0, DOI 10.1186/s13054-019-2539-x, DOI	2019	10.61	2020	2024	
Krammer F, 2018, NAT REV DIS PRIMERS, V4, P0, DOI 10.1038/s41572-018-0002-y, DOI	2018	8.39	2020	2024	

Fig. 6 (**A**). Top 10 co-cited publications. (**B**). Network of co-cited publications cited at least 50 times. (**C**). Top 15 articles by citation burst strength

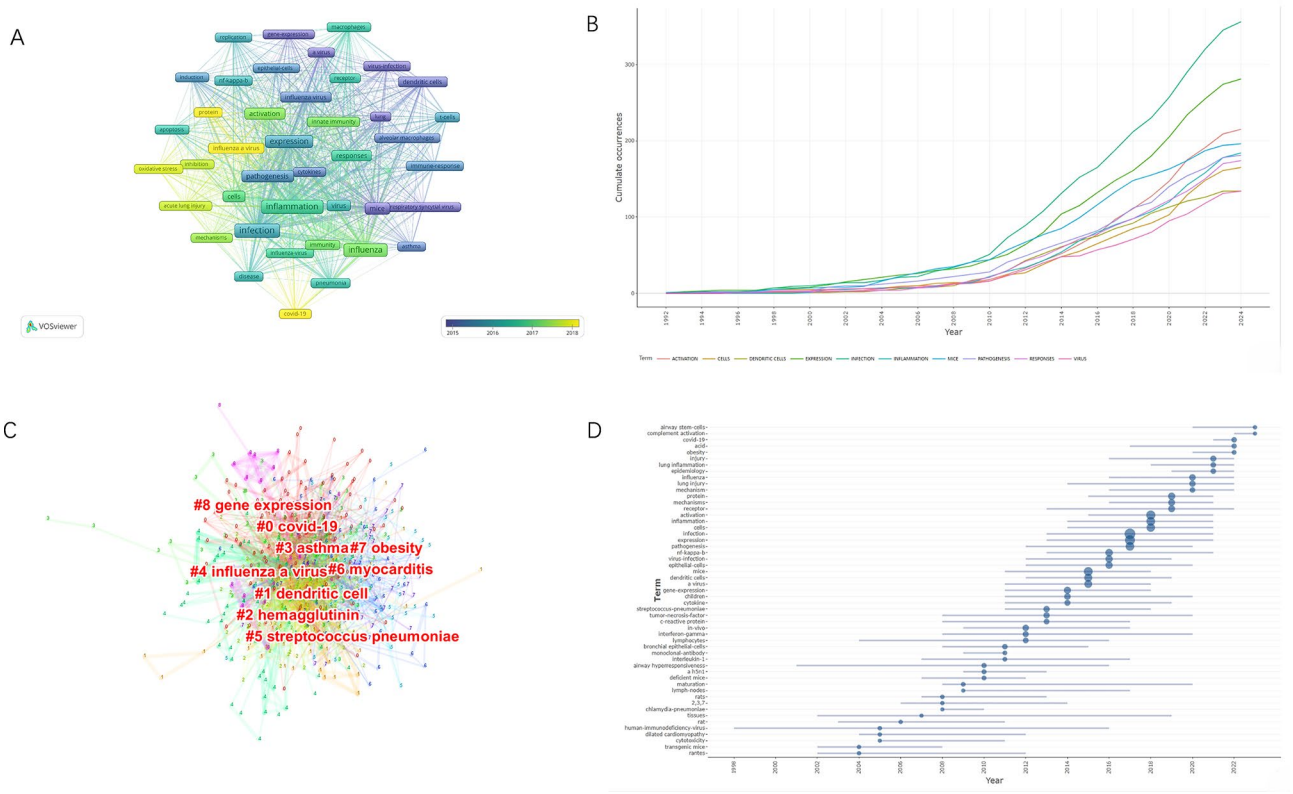


Fig. 7 (**A**). Keyword co-occurrence network diagram. (**B**). Cumulative occurrence count of keywords. (**C**). Keyword co-occurrence clustering map. (**D**). Trend map associated with influenza inflammation response

Table 4 Top 10 most frequently occurring keywords

Rank	Keywords	Counts	Rank	Keywords	Counts
1	infection	405	6	activation	216
2	inflammation	396	7	pathogenesis	201
3	influenza	337	8	responses	174
4	expression	281	9	cells	165
5	mice	217	10	virus	160

all the key terms (Fig. 7C). The top 3 clustered key terms included covid-19, dendritic cell, and hemagglutinin. Furthermore, the mechanism of action of airway stem cells and complement activation has been a trend in influenza research in the past two years, providing new directions and ideas for the treatment targets of influenza complications (Fig. 7D).

Discussion

In this study, five tools were applied to draw bibliometric maps and visualization images for 2,176 articles. The current state of research and emerging trends of influenza inflammatory responses were systematically assessed through quantitative, qualitative, and comprehensive research methods. Notably, this is the first bibliometric study in this research field.

General information

The volume of articles in the research field has gradually increased, with explosive growth detected after 2009 and 2019. The number of articles published yearly since 2015 has exceeded 110 (R^2=0.8707), indicating that the study of inflammatory response in influenza has significant research value. The United States ranks first in publications (928 articles), mainly due to the high productivity of St. Jude Children's Research Hospital (52 articles) in this field. China and the United Kingdom rank second and third with 450 and 158 articles, respectively. The United States showed close collaborations with several countries/regions, such as China and Canada. Additionally, most countries and researchers cooperated with China, Australia and Canada. However, many countries have little or no collaboration in this field (Fig. 3A −3B). Professor Ross Vlahos published the most related literature (22 articles). Most articles are published in the PLoS One (95 articles). Furthermore, 6 of 10 most highly cited periodicals had impact factors higher than 10, indicating high research quality in this field.

Knowledge base

Influenza virus is a part of the Orthomyxoviridae family. This family is characterized by viral glycoproteins including hemagglutinin (HA) and neuraminidase (NA), which

determine the virus subtypes [32]. The influenza virus is effectively prevented by the robust defense mechanism of the innate immune system. Pattern recognition receptors (PRRs) identify pathogen-associated molecular patterns (PAMPs) [33], leading to the secretion of interferons (IFNs), pro-inflammatory cytokines, eicosanoid, and chemokines [34, 35], thus detecting viral infections. Studies have shown that the 1918 influenza virus also exhibits high pathogenicity in mice. Studies have also verified the multi-genic origin of this virulence phenotype [36]. Darwyn Kobasa showed that the 1918 influenza virus can cause severe respiratory infections in primate cynomolgus macaque models, thereby leading to acute respiratory distress or even death [37]. Additionally, infection dysregulates antiviral response in animals, suggesting that an atypical host innate immune response may accelerate mortality [38]. Influenza virus can modulate host immune responses, a common feature of pathogenic influenza viruses.

Severe complications caused by pandemic influenza or high pathogenic (HP) H5N1 avian influenza virus are associated with rapid and massive infiltration of inflammatory cells [39]. Menno D de Jong et al. conducted virological and immunological studies on 18 H5N1 patients and eight individuals with human influenza virus subtypes to assess the correlation between high viral replication and virus-induced cytokine dysregulation with disease severity in humans. The research findings revealed that individuals infected with human H5N1 influenza exhibit elevated viral loads within the throat region, while viral RNA is present in the rectum and bloodstream. Furthermore, a decrease in peripheral blood T lymphocyte counts is observed in these cases, alongside high concentrations of chemokines and cytokines. Notably, this elevation is more pronounced in deceased patients, which correlates with the viral load detected in their throat samples [30]. This study suggests that the primary cause of H5N1 influenza lies in the high viral loads and subsequent intense inflammatory response. The severe damage caused by the excessive inflammatory response during IAV infection is able to cause life-threatening lung diseases. Both HP virus and H5N1 avian influenza viruses can induce a cytokine storm characterized by dysregulation and overproduction of inflammatory cytokines. The aforementioned consequences are linked to the occurrence of severe pulmonary edema, both primary and secondary pneumonia, as well as alveolar hemorrhage in cases of acute bronchopneumonia [40, 41]. Researchers have employed flow cytometry to assess the cellular immune response in mouse lung infections caused by HP H1N1 and H5N1 influenza viruses. The results indicate a substantial rise in the quantity of macrophages and neutrophils present in the infected lungs. Macrophages and neutrophils can rapidly accumulate in the lungs due to HP influenza viruses. The HP influenza virus infection is linked to acute pulmonary inflammation, and these cells are essential in this process [42].

Macrophages and neutrophils are capable of releasing chemokines and cytokines, which act in an autocrine manner. The production of chemokines at the site of infection leads to the recruitment of additional immune cells, such as neutrophils, monocytes, and natural killer (NK) cells, to the airways. These recruited immune cells target virus-infected epithelial cells for NK cell-mediated virus clearance [43]. Influenza virus-infected lungs recruit monocytes and neutrophils quickly to eliminate infected and dying cells [44]. Monocytes/macrophages infected with viruses can generate pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor-alpha, and interferon-alpha (IFN-α). This process results in the enhanced expression of chemokines MCP-1, MCP-3, and IP-10. Consequently, this amplification of inflammatory/chemotactic signals leads to the recruitment of more monocytes/macrophages and T lymphocytes to the site of infection [45]. Virus-infected macrophages not only trigger a potent pro-inflammatory response but also cause significant tissue damage by releasing excessive amounts of reactive nitrogen intermediates and reactive oxygen species (ROS). These harmful substances cannot differentiate between foreign pathogens and the body's own cells, leading to collateral damage. The overproduction of reactive nitrogen intermediates and ROS can lead to widespread tissue damage [46].

Emerging topics

Two immune responses of dendritic cells (DCs) to IAV are the research focus and hot topic in this field. In addition, the relationship between airway stem cells and lung injury treatment is increasingly becoming a research focus. The progenitor cell characteristics of airway basal stem cells suggest their potential in lung tissue regeneration medicine, attracting much interest in this field. Furthermore, the COVID-19 pandemic significantly impacted humans, necessitating response measures to mitigate losses. Given the high variability of influenza strains, continuous monitoring of the effectiveness of existing antiviral medications is crucial. Furthermore, the urgent discovery of new anti-inflammatory drugs to mitigate influenza-related inflammatory diseases is required.

DCs are a unique subset of hematopoietic mononuclear cells and professional antigen-presenting cells (APCs), serving as key mediators for congenital immunity and specific immunity to IAV infection [47]. DCs are located in secondary lymphoid organs and peripheral sites/surfaces. DCs are typically subdivided into two main subsets, including plasmacytoid DCs (pDCs) and conventional DCs (cDCs). pDCs are the major producers

of the antiviral cytokine IFN-α. cDC1 and cDC2 are two critical mediators of cytotoxic T lymphocyte (CTL) responses to IAV infection [48]. Respiratory dendritic cells (RDCs) are targets during influenza virus infection. RDCs migrate from the lungs to draining lymph nodes, as the primary APCs, to induce adaptive immune CD8 T cell responses to viral infection [49, 50]. Studies have shown that cDC1 depletion results in insufficient specific primary $CD8^+$ T cell activation and significant inflammation in lung, which can impair $CD8^+$ T cell immunological memory activation and cross-reactivity. This reactive pattern reveals that cDC1 participates in the activation of primary T cells and the proliferation of effective memory $CD8^+$ T cell precursors [51]. DCs provide the first line of defense after IAV infection, thus linking innate and adaptive immunity. Many DC populations can elicit immune responses to IAV in infected lung tissues and associated lymph nodes [52]. Besides, H1N1 influenza virus can induce abnormal arginine metabolism in nasal mucosal epithelial progenitor cells, leading to inflammation, promoting the maturation and recruitment of DCs in the nasal mucosa, thereby triggering mucosal immunity in the respiratory tract [53]. Models for DC immunotherapy, both in vivo and in vitro, have shown the significance of DCs in detecting IAV [54].

Various lung stem cells/progenitor cells are found in different ecological niches throughout the lung. These cells mediate site-specific responses to injury. Basal stem cells in the proximal airways, as resident stem cells, can self-renew in a steady state and after acute injury, repopulating nearly all cell types of the pseudostratified epithelium [55]. The remaining basal stem cells rapidly increase their proliferation rate and differentiate within the first 24 h to restore lung homeostasis when exposed to acute injury from physical injury, chemical injury, or pathogen infection [56]. Additionally, researchers have found that mice and human airway basal stem cells can sense hypoxia, triggering these stem cells to differentiate directly into solitary neuroendocrine cells. NE cell hyperplasia occurs in various lung diseases, such as asthma, congenital pneumonia, pulmonary arterial hypertension, and chronic obstructive pulmonary disease (COPD), representing a compensatory physiological response [57]. The protective peptide calcitonin gene-related peptide (CGRP) secreted by neuroendocrine cells can improve excessive damage during hypoxia, while the removal of these cells can exacerbate injury, suggesting that different forms of lung injury may elicit distinct protective NE cell responses [58]. Transplantation of basal-like cells derived from mice primary or human primary pluripotent stem cells (PSC) into genetically matched or NOD scid gama (NSG) recipient mice with polidocanol injury can achieve long-term self-renewal and sustained multipotent differentiation in vivo for at least 2 years [59]. These findings provide insights for future therapies for patients with diseases caused by airway epithelial cell injury or dysfunction.

The novel coronavirus infection is an acute infectious disease caused by a novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2). In March 2020, The World Health Organization declared that SARS-CoV-2 has pandemic characteristics [60]. The main clinical symptoms of patients with SARS-CoV-2 are fever, dry cough, and fatigue. Critically ill patients may experience breathing difficulties, acute respiratory distress syndrome, septic shock, multiple organ failure, and other manifestations [61]. The rapid, continuous, and unpredictable evolution of influenza viruses promotes the variability of its pathogenesis, posing challenges for influenza vaccine development and pandemic preparedness. Many basic control measures for pandemics are based on seasonal influenza measures. Therefore, establishing a sustainable global influenza vaccine production network and supply chain is crucial. Furthermore, encouraging and investing in research and development of influenza and respiratory pathogens, sustainable funding for research and innovation are necessary. Lastly, building trust, improving communication, and implementing intervention measures for patients and the public are essential [62, 63].

Mehdi Rabie-Rudsari et al. identified NA mutations in the A/H1N1 and A/H3N2 subtypes of influenza A in samples collected from Mazandaran, Iran, between 2016 and 2020. Although no mutations related to oseltamivir resistance were detected, notable differences were observed in the NA gene compared to vaccine strains. A total of 43 mutations were identified in the A/H1N1 subtype, while 66 mutations were found in the A/H3N2 subtype [64]. These findings underscore the importance of continuous monitoring for drug-resistant mutations. Recent research has demonstrated that oclacitinib, a representative compound of Janus kinase (JAK) inhibitors, effectively inhibits neutrophil and macrophage infiltration, reduces the production of pro-inflammatory cytokines, and ultimately alleviates lung damage in mice infected with a lethal strain of the influenza virus, without affecting viral titers. The efficacy of 10 JAK inhibitors was assessed using an influenza mouse model, revealing that 7 of these compounds exhibited a protective efficacy ranging from 40 to 70% against lethal influenza virus infection [65]. These results suggest that JAK inhibitors can modulate the immune response to influenza virus infection and may represent a potential treatment option for influenza.

In summary, influenza induces a systemic inflammatory response through the activation of the immune system. While this response is essential for combating the virus, excessive inflammation can lead to significant health

complications. During the recovery phase from influenza, although the virus is cleared, the inflammatory response may persist, resulting in continued fatigue and weakness. C-reactive protein (CRP), recognized as a biomarker for various diseases, has the potential to contribute to our understanding of systemic inflammation. Recent advancements in diagnostic algorithms have demonstrated the ability to accurately diagnose diseases by assessing CRP levels, which holds considerable significance for understanding influenza and its associated inflammatory reactions [66].

Limitations

This study has the following two levels of limitations. First, this study only contains articles from core data set of the Web of Science data base, including only English publications. Additionally, the selection process may not be perfectly refined.

Conclusion

The comprehensive analysis suggests that inflammation and its mechanisms are crucial in the damage caused by influenza. Additionally, cytokine storms and immune responses also contribute significantly to this damage. Notably, the United States, China, and the United Kingdom are the top three countries making important contributions to this research area. Notably, St. Jude Children's Research Hospital has the highest number of publications in this area. Ross Vlahos from the School of Health and Biomedical Sciences at RMIT University is the most prolific author in this field. Dendritic cells, airway stem cells, and neuroendocrine cells assume pivotal roles in the treatment of influenza.

Author contributions

HL and YPZ. wrote the main manuscript text and JJL, ZZ and YLC: prepared the acquisition, analysis. JCG and WBS: revised the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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