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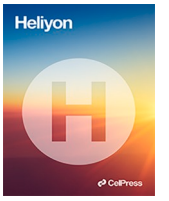

Global research trends of immunosenescence: A bibliometric study

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ABSTRACT

Background: Immunosenescence, an age-related deficit in immunity, associated with multiple disorders and making the successful aging a challenge. Although nearly 4000 articles have been published, only few review articles have summarized the research status. In order to better understand the most recent advances, hotspots and development trends in immunosenescence, it is very necessary to conduct a comprehensive bibliometric analysis. Hence, commonly used bibliometric analysis software CiteSpace and VOSviewer were employed to conduct a quantitative analysis and critical evaluation of publications in this study.

Methods: Immunosenescence publications were screened from the Web of Science Core Collection (WoSCC). Microsoft Excel 2021, CiteSpace 5.8.R3, and VOSviewer 1.6.17 were used for bibliometric study.

Results: A total of 3875 publications were retrieved from WoSCC. After screening by document type (article or review) (352 publications were excluded) and language of English (85 were excluded), 3438 studies were finally used for bibliometric analysis. The literature on immunosenescence had been continuously growing since 1991, and by 2020 it has skyrocketed 312 publications from 240 in 2019. USA (1111 publications, 35.01%) was the leading country of publications, followed by ITALY (379, 11.94%) and ENGLAND (366, 11.53%). Of the authors, Pawelec G from the Tubingen University of GERMANY contributed the greatest articles (93 publications). All the keywords could be divided into five clusters, and additional potent visualization bursts revealed that "gut microbiota," "health," "dysfunction," and "nivolumab" were the active hotspots presently.

Conclusion: Based on the current data, we firstly concluded that there will be a dramatically rising publications on immunosenescence, and research teams from USA or GERMANY might be the best chooses for collaboration. Moreover, We particularly emphasized the development potential of mechanism and intervening strategies like "gut microbiota" and "nivolumab" in immunosenescence. We hope to provide new ideas for promoting the basic research and clinical application of immunosenescence.

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1. Introduction

Immunosenescence refers specifically to the age-related changes in immunofunction and subset composition, which are associated with a host of senile diseases and make the successful aging a challenge [1]. It has always been a goal of medical research and health policy to strive for longevity worldwide, and in fact, people have significantly lived longer but not healthier [2]. The immunologic hypothesis of ageing, proposed by Roy Walford in 1969 in a seminal book named "The immunologic theory of aging", suggested that immune-mediated tissue damage generally plays a significant role in ageing. This work was extremely helpful in highlighting the interaction between ageing and the associated changes in immunity [3]. With this, Yousefzadeh et al. selectively deleted *Ercc1* (a crucial gene encoding DNA-repair protein) to construct an immunosenescence mice model and found that Vav-iCre+/−; Ercc1-/fl showed immunological phenotypes that were identical to those of elderly wild-types, and other solid organs also exhibited enhanced senescence. This suggested that the immune system can drive systemic ageing and may be a major therapeutic target for extending healthy longevity [4]. Therefore, understanding the mechanisms of age-related deficits in immunity is important to identify more efficient strategies for immune rejuvenation and anti-aging.

Over the past decades, accumulated evidence has indicated that immunosenescence is implicated in the occurrence and development of multiple diseases, such as cancer [5], neurodegenerative diseases [6], infectious diseases [7], and multiple sclerosis [8]. Sufficient studies have demonstrated that immunosenescence is of prognostic relevance of many diseases, can predict mortality in 3-year mortality more accurately, independently of other measures of health status [9]. In addition, immunosenescence can increase the risk of infection and mortality, which is of particular importance to infectious disease like COVID-19 in the elderly [10]. Although mRNA COVID-19 vaccines have proven highly effective in the elderly (the Pfizer vaccine and the Moderna vaccine has a success rate of 95% and 86% in people over 65 years old respectively), *anti*-SARS-CoV-2 antibodies in people over 80 still less than in those under 60 [11]. Therefore, it is essential to develop potent immunosenescence intervening strategies with high potential for preventing and treating the abovementioned diseases. In fact, sufficient studies of immunological differences between young and old individuals soon led to the efforts to immune rejuvenation system, and several strategies like physical activity, caloric restriction, and PD-1 inhibitors that can ameliorate immunosenescence [12–14].

In recent years, immunosenescence has received unprecedented attention worldwide, and thousands of related records in this field have been published. From the literature available, some offered a cross-sectional study of the immunological differences between the young and old, whereas others mainly focused on its mechanisms and relationship with various pathological conditions. Existing reviews also summarized only the topics mentioned above, but no attempts have been made to investigate the outputs and research status comprehensively from a global perspective. Thus, it is essential to reveal the current status, future trends, and hotspots in immunosenescence.

Bibliometric analysis, a branch of informaticsis and an effective tool for objectively studying the status quo and reflecting the development of a scientific field [15,16]. It conducts quantitative analysis based on the information available in posted records, including journals, published times, authors, institutions, affiliated countries, keywords et al. [17,18]. However, it seems very difficult to manually extract information and systematically analyze the research stats in a field, due to a large number of publications have been published after years of development. So, it is necessary to use reliable analytical tools. Recently, CiteSpace and VOSviewer, two popular bibliometric analysis tools, have been widely used in various academic research fields, such as Single-Cell Sequencing Technology [19], electrochemiluminescence sensing technology [20], regenerative medicine [21], mesenchymal stem cells [22], Alzheimer's disease with toxic pesticide environmental exposure [23], and ferroptosis [24]. CiteSpace is a Java-based software for literature analysis in a specific field and explore the development trend of related disciplines by drawing a series of visual atlases based on collaborative analysis theory and pathfinding network scale [25,26]. It has some unique concepts, such as centrality, burst detection, internumber and heterogeneous networks, which helps to identify the nature of research frontiers, emerging trends and sudden changes in time, and facilitates a comprehensive analysis of the development in this field [27,28]. Moreover, VOSviewer can build a more intuitive visual map for countries' cooperating network and keywords clustering analysis [16].

In this study, we performed a bibliometric analysis based on publications on immunosenescence from 2001 to 2021, which could provide important information on the latest developments, evolution process, international research hotspots, and future trends in immunosenescence. CiteSpace and VOSviewer were combined to perform mathematical and statistical analyses, and generate further visualization maps of different node types, such as countries, institutions, journals, and keywords etc.

2. Materials and methods

2.1. Source database and search strategy

The Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (AHCI), Conference Proceedings Citation Index Science (CPCI–S), Conference Proceedings Citation Index Social Science & Humanities (CPCI-SSH), Emerging Sources Citation Index (ESCI), Current Chemical Reactions (CCR-EXPANDED), Index Chemicus (IC) of Web of Science Core Collection (WoSCC) databases were selected as the source database. Bibliographic retrieval was conducted by two independent authors on a single day (January 16, 2022) using the following search strategy: TS = ("immunosenescence" OR "immune senescence" OR "senile immunity" OR "immuno-aging"). Search literature with the time span of all years (−2022.01.16). For the document type filter, only English language articles or reviews were included, and all other types were excluded.

2.2. Data extraction and visualized analysis

All results were searched using the above strategy and the whole record content and cited references were exported in TXT format. The count of publications and citations, journal impact factor (IF), and Journal Citation Reports (JCR) quartile in the category were also collected and imported to Microsoft Excel 2021 for statistical analysis. General research tendency and influence of an individual, institution, or country/region were reflected by a count of publications and citations. IF and JCR category data are two significant markers of the scientific "prestige" of a journal or article. IF presents the average citation number of each article for a journal during the last 2 years and is updated annually, and the JCR category is the quartile rank of journals in specific fields based on their IF.

In this study, CiteSpace 5.8.R3, a powerful visualization tool for intuitively identifying current hotspots and future research trends, was used for: (i) building the specific network and/or analyzing the number of publications of countries, institutions, authors, and journals, (ii) creating a dual-map overlay of journals, and (iii) capturing strongest citation burst of keywords and references. For all visualizations, time slicing was set from Jan 2001 to Dec 2021, and other parameters were set in default. Additionally, the java-based VOSviewer 1.6.17 was used for countries' cooperating network and keywords clustering analysis, with a minimum number of occurrences of a term as 50.

3. Results

3.1. Retrieval results

A total of 3875 publications were retrieved from WoSCC. After screening by document type (article or review) (352 publications were excluded) and language of English (85 were excluded), 3438 studies were finally identified for bibliometric analysis (Fig. 1).

3.2. Publication outputs and citation trend

Publications and citation counts in a certain period represent the development trend of a field. As shown in Fig. 2, search results showed that the first publication on immunosenescence appeared in 1980, and there were 0–3 publications per year before 1991. From 1991 to 2001, the count of papers fluctuated increasingly indicating that the field concerning immunosenescence has begun to receive attention, but the development is very uneven. From 2001 to 2009 and 2010 to 2014, publication output during these two periods steadily increased. And from 2014 to 2016 and 2017 to 2019, the researches were at a brief standstill. Until 2020, the number of publications has exploded and reached 312 from 240 in 2019. The number of cited times was only 0 to 10 before 1990. The number of citations increased gradually from 1991 to 2009, quickly from 2009 to 2019 and suddenly from 2019 to 2021, reaching 18,915 as of 2021.

3.3. Contributions of countries/regions

A total of 98 countries/regions contributed to the research of immunosenescence (Supplementary Table 1). As can be seen from Table 1, the highest number of publications came from the USA (1111, 35.01%), which is far more than three times higher than the

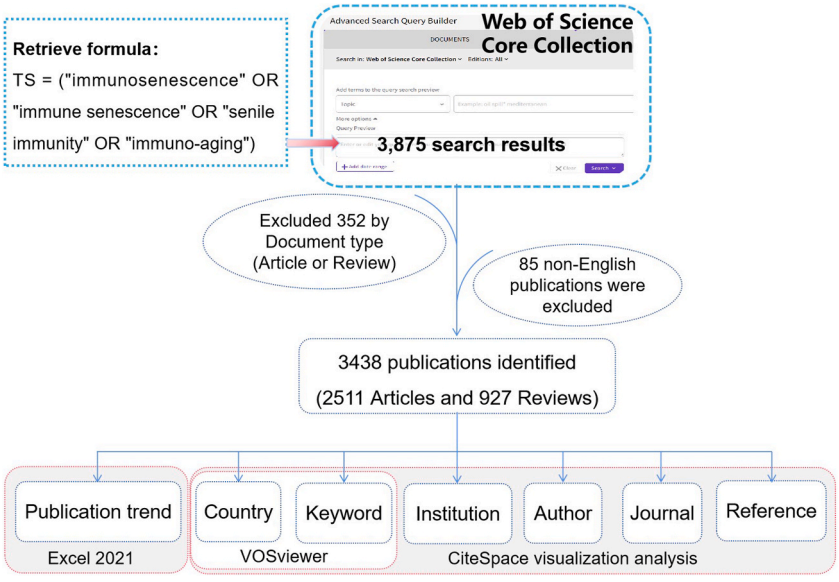

Fig. 1. Flowchart for the screening of publications in this study.

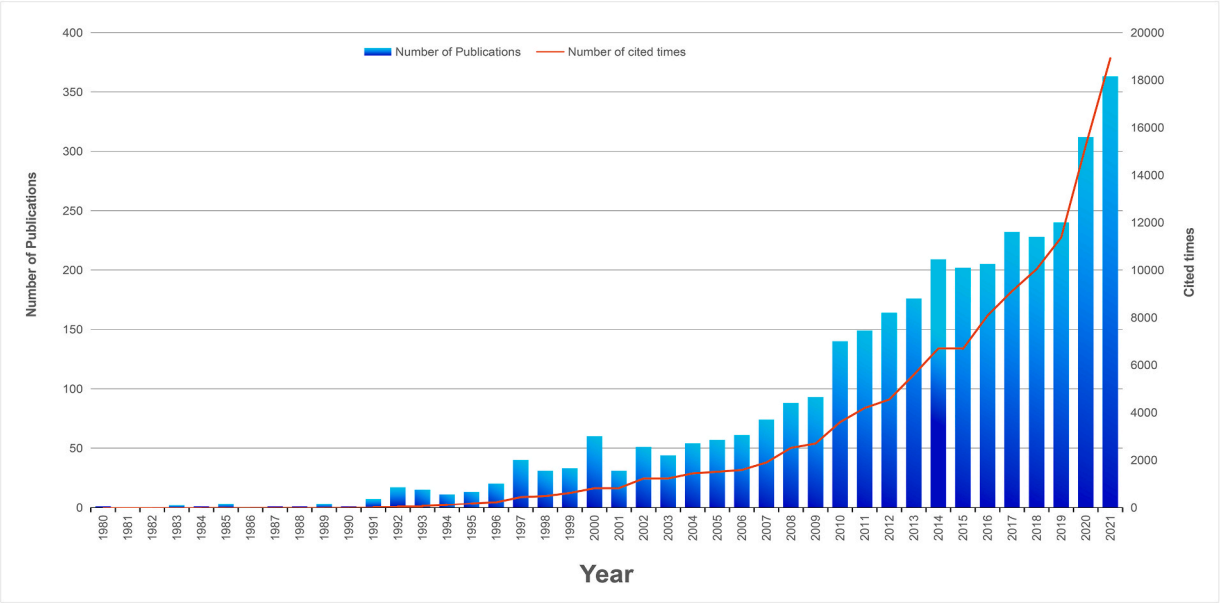

Fig. 2. The number of publications and citation times of immunosenescence worldwide.

following: ITALY (379, 11.94%) and ENGLAND (366, 11.53%). Of the top 10 countries/regions, 60% of the centrality is greater than or equal to 0.1, such as the USA (0.4), ENGLAND (0.23), ITALY (0.15), FRANCE (0.13), GERMANY (0.11), and CANADA (0.1), indicating that countries with higher publications have conducted active cooperation. The collaboration network map of Fig. 3 also indicates that cooperation among countries/regions was relatively close (lines denote cooperation between countries/regions). VOSviewer was further used to visualize the cooperation network of the top 20 countries (ranked by the number of publications) and found that the USA collaborated most closely with GERMANY, ENGLAND, and ITALY (Fig. 4).

3.4. Contributions of institutions

In total, 595 institutions made contributions to immunosenescence (Supplementary Table 2). The top 10 research institutions ranked by number of publications are listed in Table 1, among them, Univ Tubingen of GERMANY contributed the most with 115 publications with the centrality of 0.21 (which is equal to Univ Cordoba of the SPAIN). Further, institutions from the USA (30%) and ITALY (20%) have made great contributions to the research of immunosenescence, publishing a total of 119 and 120 articles, respectively. In addition, only Univ Tubingen of GERMANY, Univ Cordoba in the Spain, the Univ Palermo of ITALY showed a higher centrality of 0.21, 0.21, and 0.15 respectively. The institution's collaboration network was visualized by CiteSpace (Pruning by pathfinder with pruning sliced networks and the inegrated network pruning). As shown in Fig. 5, this cooperation map, including 595 nodes and 1627 links (only institutions greater than or equal to 10 publications were visualized), indicated an active collaboration among these institutions.

3.5. Contributions of authors

A total of 793 authors were involved in the 3173 publications. As shown in Table 2, the top 10 most productive authors contributed

Table 1
Top 10 countries/regions and institutions related to immunosenescence.

Rank	countries	count	centrality	Institutions	Count	Centrality	Country
1	USA	1111	0.4	Univ Tubingen	115	0.21	GERMANY
2	ITALY	379	0.15	Univ Bologna	69	0.04	ITALY
3	ENGLAND	366	0.23	Univ Sherbrooke	56	0.07	CANADA
4	GERMANY	330	0.11	Univ Birmingham	53	0.02	ENGLAND
5	SPAIN	243	0.08	Univ Palermo	51	0.15	ITALY
6	CANADA	193	0.1	Stanford Univ	45	0.02	USA
7	FRANCE	165	0.13	ASTAR	41	0.02	SINGAPORE
8	PEOPLES R CHINA	159	0.01	Univ Calif Los Angeles	38	0.05	USA
9	BRAZIL	134	0.04	Univ Sao Paulo	37	0.05	BRAZIL
10	NETHERLANDS	125	0.04	Univ Cordoba	36	0.21	SPAIN

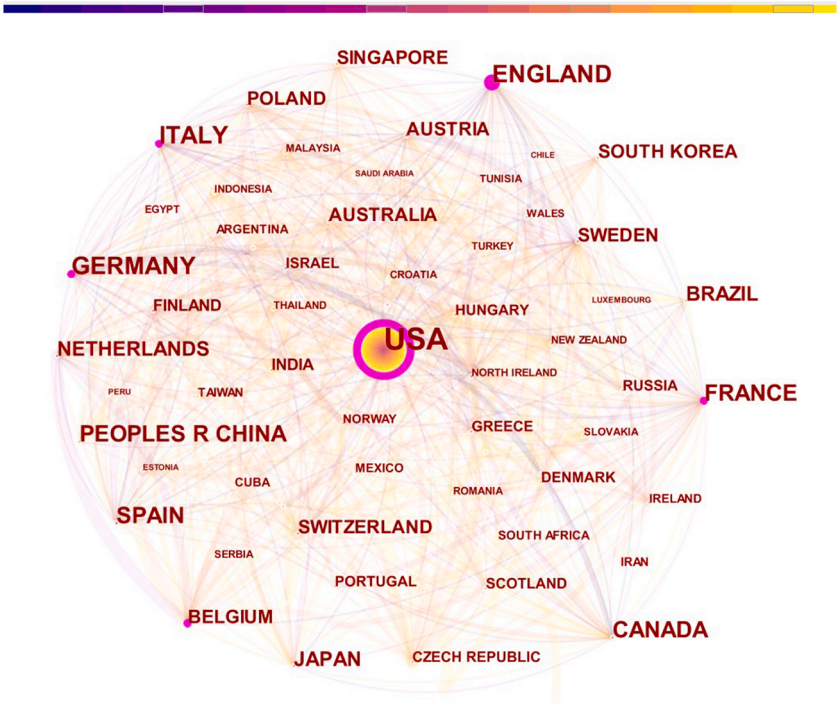

Fig. 3. Collaboration network map of countries/regions from 2001 to 2021.

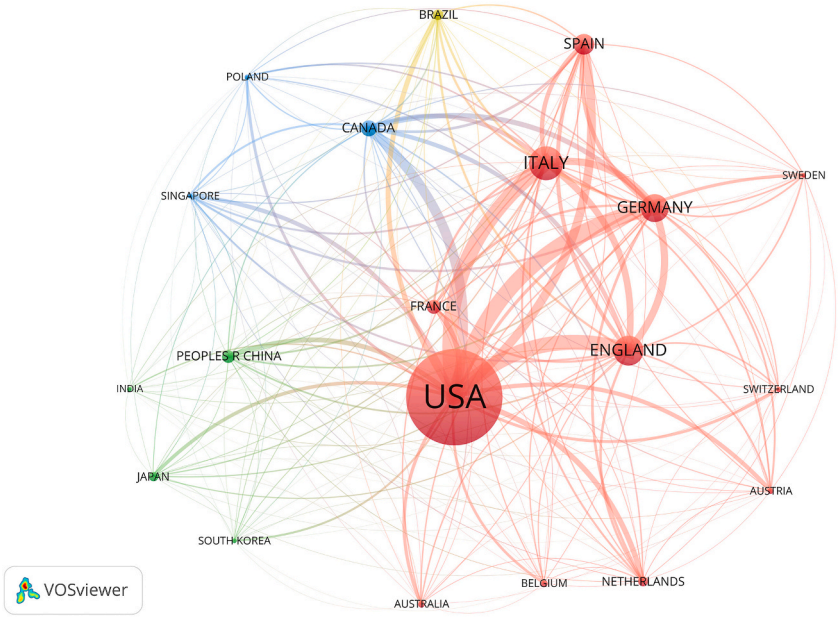

Fig. 4. Collaboration network of top 20 countries/regions (ranked by publications) of research related to immunosenescence from 2001 to 2021.

470 articles (14.81%) on immunosenescence. Pawelec G from the Tubingen University of GERMANY contributed the most articles (110 publications), followed by Larbi A from Sherbrooke University of CANADA with 66 publications. Franceschi C from the Bologna University of ITALY ranked third with 61 publications, which were cited 7410 times. From the source of the top 10 authors, Tubingen University (GERMANY) and Sherbrooke University (CANADA) were the leading institutions in immunosenescence research, with a total of 110 and 105 publications, respectively. In addition, it is possible to note that the centrality of all listed authors was low, only changing from 0.01 to 0.28. Fig. 6 shows the authors' cooperative network. This map contained 793 nodes and 1293 links (Pruning the

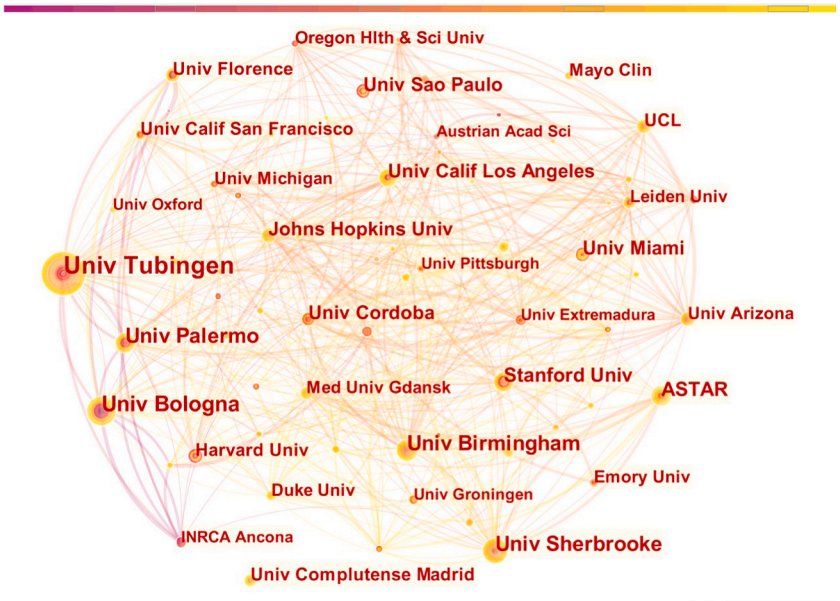

Fig. 5. Collaboration network map of institutions from 2001 to 2021.

Table 2
Top 10 authors related to immunosenescence from 2001 to 2021.

Rank	Authors	Count	Centrality	Cited Count	Country	Institution
1	Pawelec G	110	0.23	6362	GERMANY	Tubingen University
2	Larbi A	66	0.07	3999	CANADA	Sherbrooke University
3	Franceschi C	61	0.28	7410	ITALY	Bologna University
4	Caruso C	41	0.03	2367	ITALY	Palermo University
5	De la fuente M	40	0.06	847	SPAIN	Complutense University
6	Fulop T	39	0.01	2123	CANADA	Sherbrooke University
7	Solana R	32	0.04	1799	SPAIN	Cordoba University
8	Grubeck-loebenstein B	30	0.05	2666	AUSTRIA	Innsbruck University
9	Candore G	26	0.05	1544	ITALY	Palermo University
10	Goronzy JJ	25	0.03	2362	USA	Stanford University

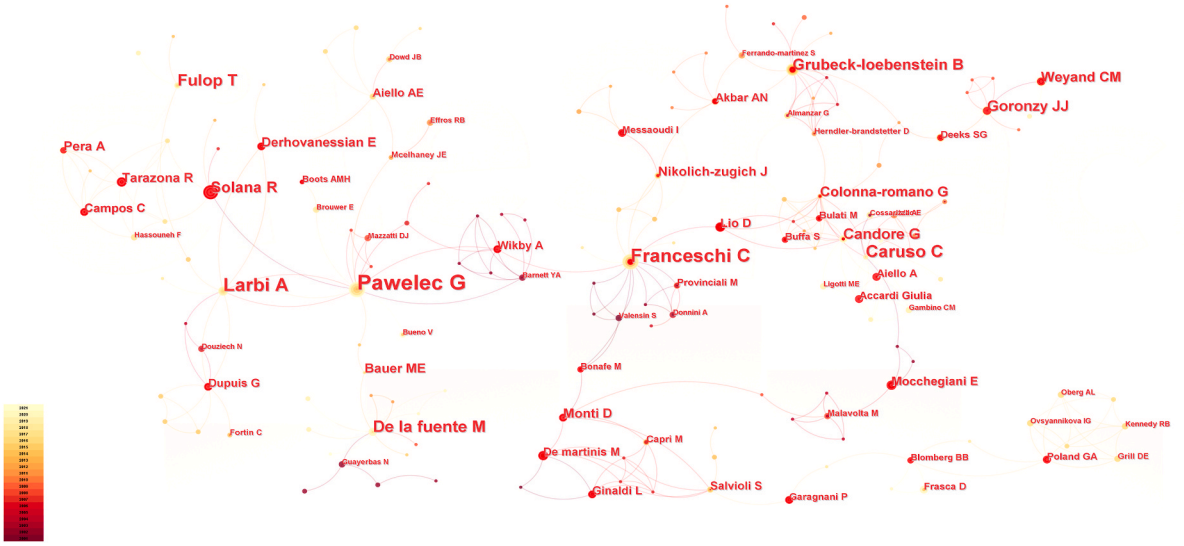

Fig. 6. Cooperative network map of authors from 2001 to 2021.

integrated network using pathfinder) and indicated that the collaboration among these 793 authors was not very active.

3.6. Contributions of journals and cited journals

A total of 1129 journals have published articles on immunosenescence. As is shown in Table 3, EXPERIMENTAL GERONTOLOGY (IF 2021, 4.253) contributed the highest number of articles (154 publications, 4.48%), followed by FRONTIERS IN IMMUNOLOGY (IF 2021, 8.786) and IMMUNITY AGEING (IF 2021, 9.701), with publications of 128 (3.72%) and 100 (2.91%), respectively. Among the top 10 journals, four quartiles in the category were Q1, four were Q2, one was Q1/Q2, and only one, Q3.

The dual-map overlay of journals demonstrated contributions and connections among journals as shown in Fig. 7. The left side of this figure presents the citing journals, the right presents the cited journals, and the colored paths between them present the cited relationships (the wider the path, the closer the relationship). There are two main paths in this figure, indicating that the documents published in journals dedicated to MOLECULAR, BIOLOGY, and GENETICS field were often cited by publications in MOLECULAR, BIOLOGY, IMMUNOLOGY and MEDICINE, MEDICAL, CLINICAL fields.

3.7. Analysis of Co-cited references and references burst

Co-citation refers to an indispensable method to measure the relationship between publications. A total of 1449 co-cited references were retrieved by CiteSpace (Supplementary Table 3). Table 4 shows the top ten most cited references, of which "Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?" written by Fulop T et al.(2018), is the most cited (120), followed by "Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases" (99) and "Understanding immunosenescence to improve responses to vaccines" (85) contributed by Franceschi C and Campisi J (2014), and Goronzy JJ and Weyand CM (2013), respectively. As shown in Fig. 8, reference with the strongest citation bursts first emerged in 2003 and was published in 2002 by Pawelec G et al. Among the top 25 most-cited co-citation references, 14/25 had been frequently cited in recent 10 years, and the most recent 5 bursts lasted until 2021, which suggested that the research of immunosenescence may continue to explode in the future.

3.8. Analysis of keywords and research hotspots

Keywords were extracted from KeyWords Plus of all the 3173 publications. A network visualization map of keyword co-occurrence analysis was generated by VOSviewer with the minimum number of occurrences greater than 50 times, which results in 73 keywords in the map after merging some thesaurus keywords (Fig. 9). All the keywords could be divided into five clusters (different colors present different clusters), which represented five major directions in the research of immunosenescence. Cluster green, with the biggest node immunosenescence (663 times), was followed by age (465 times) and inflammation (240 times). The red one including 25 keywords was the largest cluster, of which T-cells (296 times), immune system (215 times), and dendritic cells (176 times) were the primary keywords. Prominent keywords of the yellow cluster were expression (352 times), activation (224 times), and responses (164 times). As for the purple cluster, the primary keywords were infection (246 times), memory (120 times), and subsets (94 times). The biggest node of the blue cluster was immune-response (197 times), which is closely related to many keywords in this cluster, such as influenza vaccine (145 times), antibody-response (69 times), and virus (62 times). The keywords with the strongest citation bursts were another important indicator to understand the research hotspots and emerging trends over time (Fig. 10). Most notably, lymphocyte was the first citation burst keyword with the highest strength 17.83, which began in 2001 and ended in 2006. The centenarian (2001–2009), *in vivo* (2002–2010), cytokine production (2002–2010), and innate immunity (2006–2014) lasted the longest with 9 years, indicating that these keywords had made great contributions to the study of immunosenescence. In addition, the citation burst time of gut microbiota (2018–2021), health (2018–2021), dysfunction (2018–2021), and nivolumab (2018–2021) have continued to 2021, suggesting that these keywords also have the potential to become next research hotspots in the future, especially the gut microbiota (strength of 13.05).

Table 3
Top 10 journals of immunosenescence ranked by publication count.

Rank	Journals (1129)	COUNT	IF	Quartile in category(2021)
1	EXPERIMENTAL GERONTOLOGY	154 (4.48%)	4.253	Q2
2	FRONTIERS IN IMMUNOLOGY	128 (3.72%)	8.786	Q1
3	IMMUNITY AGEING	100 (2.91%)	9.701	Q1
4	MECHANISMS OF AGEING AND DEVELOPMENT	99 (2.88%)	5.498	Q1/Q2
5	PLOS ONE	62 (1.80%)	3.752	Q2
6	AGING CELL	48 (1.40%)	11.005	Q1
7	JOURNALS OF GERONTOLOGY SERIES A BIOLOGICAL SCIENCES AND MEDICAL SCIENCES	47 (1.37%)	6.591	Q1
8	VACCINE	47 (1.37%)	4.169	Q3
9	BIOGERONTOLOGY	46 (1.34%)	4.284	Q2
10	JOURNAL OF IMMUNOLOGY	46 (1.34%)	5.426	Q2

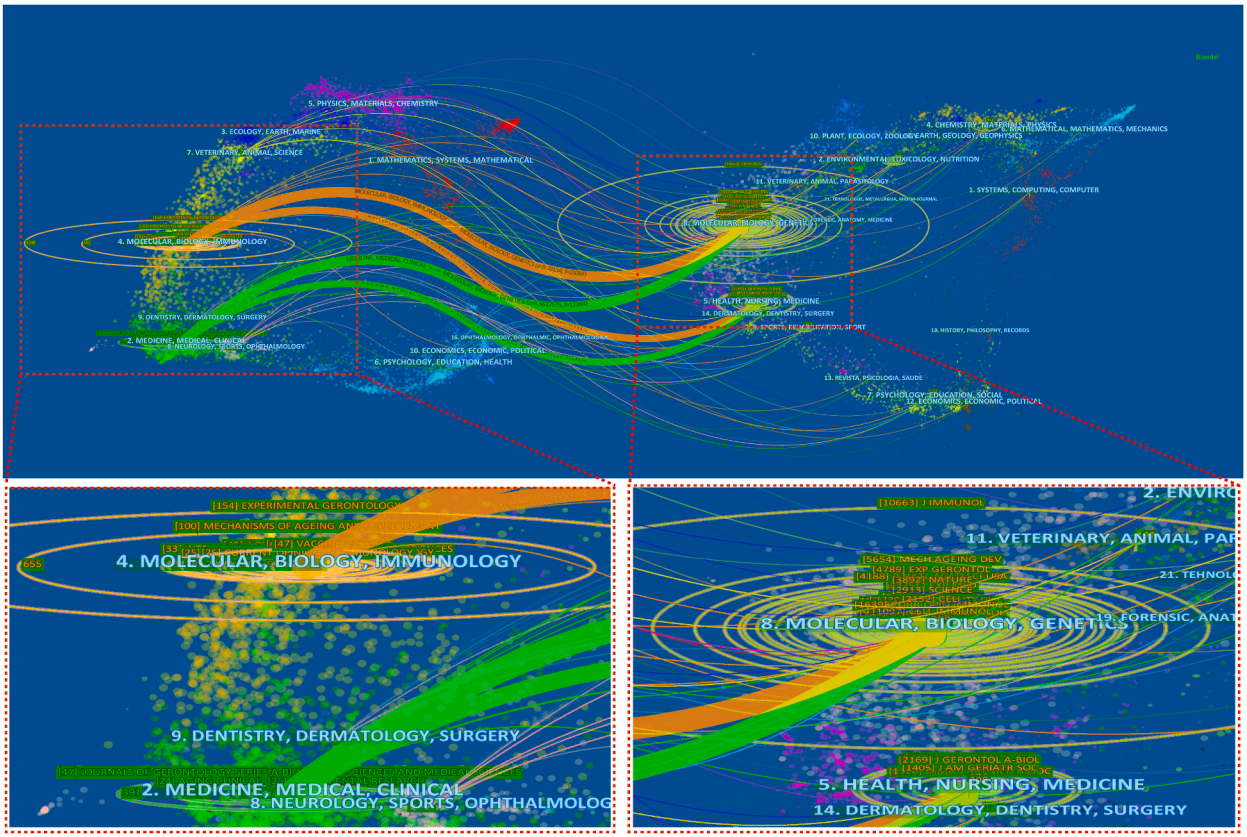

Fig. 7. The dual-map overlay of journals on immunosenescence.

Table 4
Top 10 co-cited references related to immunosenescence.

Rank	Reference	Count	(First)Author	Year	Centrality
1	Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?	120	Fulop T	2018	0.01
2	Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases	99	Franceschi C	2014	0.01
3	Understanding immunosenescence to improve responses to vaccines	85	Goronzy JJ	2013	0.01
4	The twilight of immunity: emerging concepts in aging of the immune system	73	Nikolich-Zugich J	2018	0.01
5	Innate immunosenescence: Effect of aging on cells and receptors of the innate immune system in humans	72	Solana R	2012	0.04
6	Human immunosenescence: is it infectious?	67	Pawelec G	2005	0.02
7	Cytomegalovirus and human immunosenescence	66	Pawelec G	2009	0.04
8	The Hallmarks of Aging	65	Lopez-Otin C	2013	0.01
9	Inflammaging and *anti*-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans	62	Franceschi C	2007	0.04
10	Age-dependent dysregulation of innate immunity	61	Shaw AC	2013	0.02

4. Discussion

4.1. General information

Bibliometric analysis of annual numbers and trends of literature offers a new possibility to understand the development speed and research progress of a certain field based on the information from publication records. As shown in Fig. 2, the overall publications related to immunosenescence are generally on the rise. From 1980 to 1991, several kinds of literature were published, indicating that the research on immunosenescence is in its infancy. From 1991 to 2001, the amount of literature showed a fluctuating growth, indicating that research of immunosenescence has begun to receive attention, yet the development was not stable. From 2001 to 2019, global publications exhibited a steady growth relatively. Moreover, the recent 2 years have witnessed an explosive growth, and the count of publications has reached 312 in 2020 and 363 in 2021 respectively. Thus, it can be concluded that research on

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2001 - 2021
Pawelec G, 2002, FRONT BIOSCI-LANDMRK, V7, P0	2002	22.63	2003	2007	
Linton PJ, 2004, NAT IMMUNOL, V5, P133, DOI 10.1038/ni1033, DOI	2004	21.19	2004	2009	
Pawelec G, 2004, TRENDS IMMUNOL, V25, P406, DOI 10.1016/j.it.2004.05.006, DOI	2004	21.59	2005	2009	
Pawelec G, 2005, IMMUNOL REV, V205, P257, DOI 10.1111/j.0105-2896.2005.00271.x, DOI	2005	34.16	2006	2010	
Franceschi C, 2007, MECH AGEING DEV, V128, P92, DOI 10.1016/j.mad.2006.11.016, DOI	2007	25.99	2007	2012	
Aw D, 2007, IMMUNOLOGY, V120, P435, DOI 10.1111/j.1365-2567.2007.02555.x, DOI	2007	26.51	2008	2012	
Gruver AL, 2007, J PATHOL, V211, P144, DOI 10.1002/path.2104, DOI	2007	25.6	2008	2012	
Pawelec G, 2009, REV MED VIROL, V19, P47, DOI 10.1002/rmv.598, DOI	2009	24.24	2010	2014	
Panda A, 2009, TRENDS IMMUNOL, V30, P325, DOI 10.1016/j.it.2009.05.004, DOI	2009	24.15	2010	2014	
Weiskopf D, 2009, TRANSPL INT, V22, P1041, DOI 10.1111/j.1432-2277.2009.00927.x, DOI	2009	21.27	2010	2014	
Derhovanessian E, 2009, CURR OPIN IMMUNOL, V21, P440, DOI 10.1016/j.coi.2009.05.012, DOI	2009	20.03	2010	2014	
Shaw AC, 2010, CURR OPIN IMMUNOL, V22, P507, DOI 10.1016/j.coi.2010.05.003, DOI	2010	23.15	2011	2015	
Panda A, 2010, J IMMUNOL, V184, P2518, DOI 10.4049/jimmunol.0901022, DOI	2010	22.73	2011	2015	
Deeks SG, 2011, ANNU REV MED, V62, P141, DOI 10.1146/annurev-med-042909-093756, DOI	2011	21.48	2012	2016	
Solana R, 2012, SEMIN IMMUNOL, V24, P331, DOI 10.1016/j.smim.2012.04.008, DOI	2012	30.19	2013	2017	
Goronzy JJ, 2013, NAT IMMUNOL, V14, P428, DOI 10.1038/ni.2588, DOI	2013	35.49	2014	2018	
Shaw AC, 2013, NAT REV IMMUNOL, V13, P875, DOI 10.1038/nri3547, DOI	2013	25.41	2014	2018	
Fulop T, 2013, FRONT IMMUNOL, V4, P0, DOI 10.3389/fimmu.2013.00271, DOI	2013	22.9	2014	2018	
Franceschi C, 2014, J GERONTOL A-BIOL, V69, P0, DOI 10.1093/gerona/glu057, DOI	2014	42.6	2015	2019	
Lopez-Otin C, 2013, CELL, V153, P1194, DOI 10.1016/j.cell.2013.05.039, DOI	2013	28.08	2015	2018	
Pera A, 2015, MATURITAS, V82, P50, DOI 10.1016/j.maturitas.2015.05.004, DOI	2015	22.24	2016	2021	
Pawelec G, 2018, EXP GERONTOL, V105, P4, DOI 10.1016/j.exger.2017.10.024, DOI	2018	21.25	2018	2021	
Fulop T, 2018, FRONT IMMUNOL, V8, P0, DOI 10.3389/fimmu.2017.01960, DOI	2018	46.65	2019	2021	
Nikolich-Zugich J, 2018, NAT IMMUNOL, V19, P10, DOI 10.1038/s41590-017-0006-x, DOI	2018	27.31	2019	2021	
Franceschi C, 2018, NAT REV ENDOCRINOL, V14, P576, DOI 10.1038/s41574-018-0059-4, DOI	2018	24.86	2019	2021	

Fig. 8. The top 25 references with the strongest citation bursts on immunosenescence from 2001 to 2021.

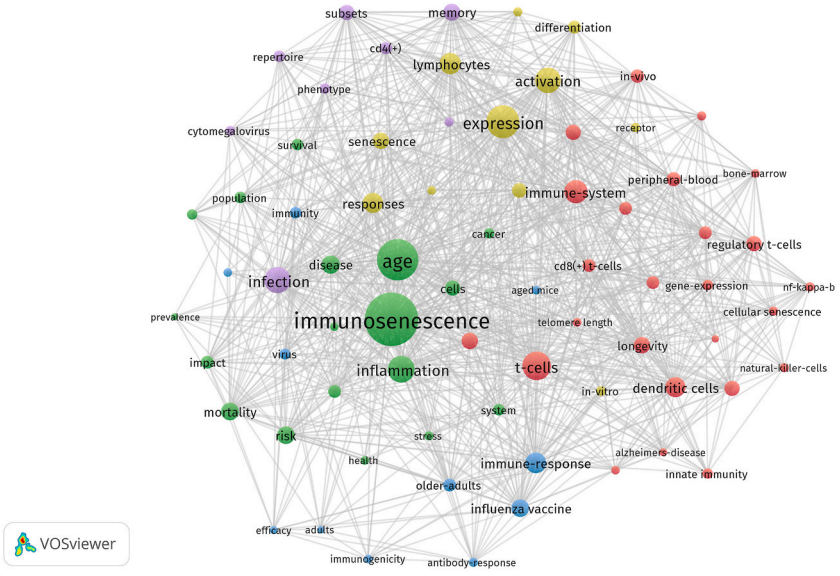

Fig. 9. VOSviewer visualization map of keywords clustering analysis related to immunosenescence from 2001 to 2021.

immunosenescence is at an advanced stage and will reach its fluorescence within the next few years.

According to the distribution of countries/regions and institutions given in Table 1, we can see that the country with the highest number of publications is the USA (1111, 35.01%), which is far more than three times higher than the following country, ITALY (379, 11.94%). Therefore, we conclude that the USA is the leading country in immunosenescence research. Generally, centrality, an index mainly used to measure the value of the bridge function of the node in the entire network structure, is considered greater than or equal to 0.1 as relatively important. Among the top 10 countries given in Table 1, the USA has the highest centrality (0.4), which means it plays a key role as a bridge in the worldwide network of state cooperation. In the list of top ten productive research institutions, Univ Tubingen from GERMANY contributed the most (115 publications), with a centrality of 0.21. Otherwise, two institutions are from the USA, and two are from ITALY. Univ Cordoba from the SPAIN and Univ Palermo from ITALY also have a high impact, with a centrality of 0.21 and 0.15 respectively. All these results suggest that the USA,GERMANY, ITALY and SPAIN has an important role in research related to immunosenescence, indicating that establishing a top-notch research institution is another pivotal basis to elevate the

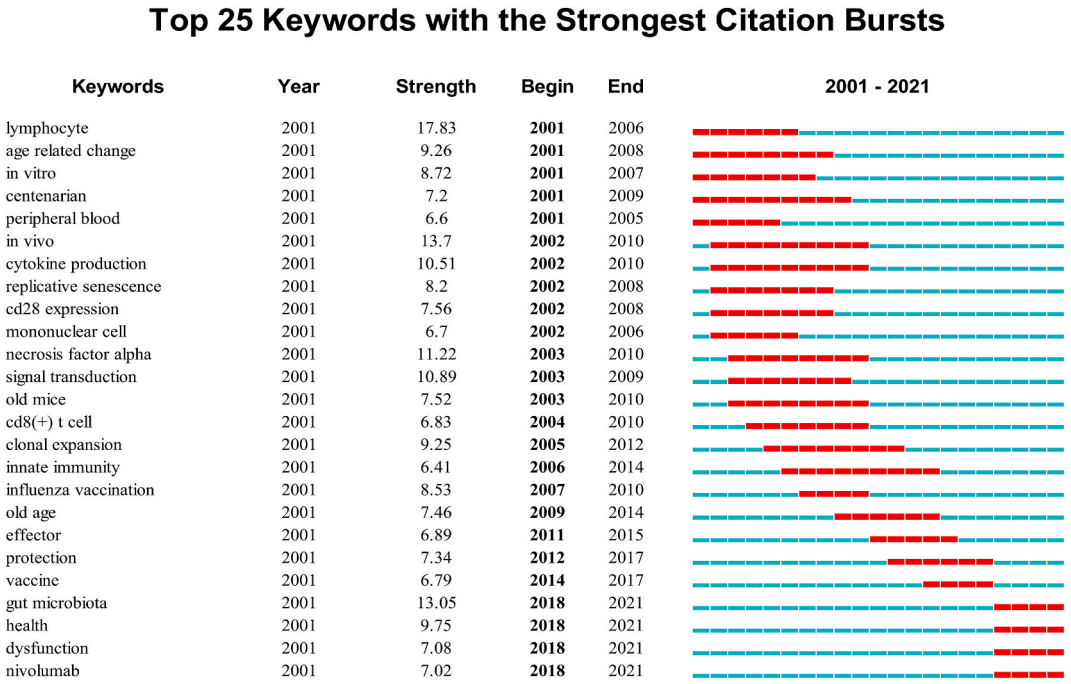

Fig. 10. The top 25 keywords with the strongest citation bursts on immunosenescence research of publications from 2001 to 2021.

academic status. Nevertheless, as evident from Figs. 3–5, although the link is relatively dense, the cooperation was not close (the wider the line, the closer the cooperation), indicating that countries/regions or institutions should further eliminate academic barriers, deepen cooperation, and promote the research related to immunosenescence.

Additionally, from the authors' contributions, Pawelec G and Larbi A has the greatest publication impact and the most outstanding contributions in the field of immunosenescence, followed by Franceschi C from the Bologna University of ITALY with 61 publications. So, further significant documents related to immunosenescence are more likely to be published by these authors or their collaborators. Hence, such individuals may be the best choices for cooperation as they may have the authentic research foundation and sufficient funding support.

Regarding the top 10 active journals listed in Table 3, EXPERIMENTAL GERONTOLOGY, FRONTIERS IN IMMUNOLOGY, IMMUNITY AGEING and MECHANISMS OF AGEING AND DEVELOPMENT were the main journals publishing research on immunosenescence, indicating that further manuscripts can refer to these journals for submission. Among the top 10 journals, four belong to Q1, four belong to Q2, one belongs to Q1/Q2, and one belongs to Q3, with the IF rate from 3.24 (PLOS ONE) to 9.304 (AGING CELL). So, it can be inferred that publishing articles related to immunosenescence in high-IF journals is still a challenge, although the research in this field has highly generated an interest around the world.

From the perspective of co-cited references, "Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?" written by Fulop T et al. (2018) has the highest citation count of 120 times, followed by "Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases" (99 times) written by Franceschi C and Campisi J (2014), as well as "Understanding immunosenescence to improve responses to vaccines" (85 times) written by Goronz, JJ and Weyand CM (Table 4). It's not difficult to suggest that the relationship between immunosenescence, inflammation, and aging has attracted considerable attention from the scientific community. The earliest burst began in 2003 owing to the article "T cells and aging, January 2002 update" published in 2002 by Pawelec G et al. and ended in 2007. This study reviewed the factors contributing to T cell immunosenescence and put forward a series of methods such as replacement therapy, supplementation therapy, gene therapy, and the like to ameliorate the dysregulated immune responses in the elderly, which laid a solid foundation for the study on immune-aging [29]. Remarkably, five bursts were from Pawelec G, and a new review "Age and immunity: What is "immunosenescence"?" from him was still in progress. Besides, there were another four review bursts currently, of these, Pera et al. (2014) summarized the molecular and cellular mechanisms with an emphasis on biomarkers, response to vaccines, and the effect of gender on immunosenescence [30]. Fulop et al. (2018) reviewed recent data on the dynamic reassessment of immune changes with aging and attempted to find ways to rejuvenate the aging immune system [31]. The remaining two most recent, strongest bursts articles were published in NAT IMMUNOL by Nikolich-Zugich (2018) and in NAT REV ENDOCRINOL by Franceschi et al. (2018), which warranted further attention. Nikolich-Zugich summarized the most recent research on the impact of ageing on immune system components, including how immune cells, soluble molecules, and lymphoid organs are affected. The importance of the metagenome and exposome in the immune system's ageing process is also highlighted [32]. Based on this, he proposed an emerging conceptual framework that age-related changes in immunity might also affect the operation rules of the older immune system, suggesting that aging and immunosenescence are two interacting plastic

processes and can be modified by interventions such as regulation of cytokine homeostasis, immune cell metabolic pathways, and naive lymphocyte production. Franceschi et al. found that gut microbiota could be a key modulator of nutrition and inflammation *via* the comparative immune-metabolic analysis of inflammation and metaflammation [33].

4.2. The hotspots and frontiers

Bibliometric analysis of keywords is also critical for revealing the developmental trends and hotspots in research related to immunosenescence. As shown in the keywords clustering map in Fig. 9, it was observed that all the keywords on immunosenescence research could be divided into five clusters. The biggest red cluster was mainly about age-related changes in the immune system, and primary keywords were t-cells, dendritic cells, regulatory t-cells, peripheral blood, and gene expression. The green cluster focused on the impact of immunosenescence and its association with other diseases, and prominent keywords were age, mortality, risk, health, disease, cancer, and survival. Blue cluster principally described the efficacy of immunoreaction with main keywords of immune-response, influenza vaccine, antibody-response, and virus. Purple clusters are mostly related to the relationship between infection and immune system, including keywords of memory, subsets, cytomegalovirus, repertoire, and phenotype. The yellow cluster was mainly about mechanisms in immunosenescence, and representative keywords were activation, differentiation, and proliferation. These findings were consistent with the developmental law of a traditional discipline, which states that a variety of rejuvenating efforts will be made after the clinical feature, molecular basis, and regulatory mechanisms of immunosenescence are gradually elucidated. Keywords with the strongest citation bursts can provide a reasonable prediction of frontiers in immunosenescence research. As shown in Fig. 10, CiteSpace V mainly captured four research frontiers: “gut microbiota”, “health”, “dysfunction” and “nivolumab”.

(1) Gut microbiota: Gut microbiota (GM), a dynamic organ, is associated with the development of several age-related diseases, such as cardiovascular disease [34], cognitive frailty [35], neurodegenerative diseases [36], and cirrhosis [37]. All these diseases are more or less attributed to the dysfunction of the aged immune system. Although many have tried to explain the action of GM in immunosenescence, and have shown that altering specific microbial composition and function can improve the immune status, yet the crosstalk mechanism between GM and immunosenescence remains unclear. Thus, further research in this field will continue to be a hot topic.
(2) Health: This keyword is mainly sourced from keywords Plus (ID), describing clinical investigation, such as age-related immune changes [38,39], immune characteristics of specific disease [40,41], and other studies about human health. This field provides not only the basic support for the research of immunosenescence but also the outcome of immunological intervention research (healthy aging). Therefore, the detailed information underlying the relationship between immunosenescence and human health is always a research hotspot.
(3) Dysfunction: Information on dysfunction, the deficit in functions of body systems, organs, and cells, was mainly obtained from keywords Plus (ID) [42]. Numerous population-based studies have shown that dysfunction in the immune system is closely related to a large number of diseases, and can severely affect a person’s health. So, understanding the mechanism behind this deficit might be a key target in promoting human health, and the crosstalk between dysfunction, and a certain disease is a research frontier [43,44].
(4) Nivolumab: Nivolumab known as a PD-1 immune checkpoint inhibitor, is approved in many countries for the treatment of cancer [45]. Research conducted over the decades have shown that T cell undergoes the most significant changes in immunosenescence. Apart from numeric defects, upregulation of immune checkpoints PD-1 have been extensively described [46]. A meta-analysis has shown that immune checkpoint inhibitors (nivolumab, ipilimumab, tremelimumab, and pembrolizumab) were significantly beneficial for both young and old patients with an age cut-off of 65–70 years. This may be caused by a potential interaction between immunosenescence and drug effect [47]. Moreover, Ferrara et al. found that circulating T cell senescence was correlated with the efficacy of PD-1 inhibitors in patients with advanced non-small cell lung cancer, but its biological mechanism remains to be clarified [14]. So, the specific effect and molecular mechanism of Nivolumab and other PD-1 inhibitors on immunosenescence must be further investigated.

According to our analysis of keywords and references, research on immunosenescence mainly focuses on the investigation of age-related changes in immunity, including keywords of age-relatedchange, centenarian, and cd28 expression. Journals in MOLECULAR, BIOLOGY, and GENETICS fields were the main source of published researches and were often cited by MOLECULAR, BIOLOGY, IMMUNOLOGY, and MEDICINE, MEDICAL, CLINICAL field journals.

In this study, we analyzed many publications from the field of immunosenescence to the present and used CiteSpace and VOSviewer metrological analysis software to conduct a visual analysis and critical evaluation. Firstly, quantitative analysis of annual publication count, country, author, institution, journal etc, indicates that immunosenescence belongs to a a gradual development field. This may be due to the growing attention paid to the relationship between immunosenescence and human health in recent years, especially since the outbreak of COVID-19. Secondly, Quantitative analysis of publications revealed that the USA and GERMANY produced the most articles, indicating these countries has an important position in research of immunosenescence. Finally, through the analysis of keywords and its’ citation burst, the main research point and development directionswere obtained, and it shown that “gut microbiota” and “nivolumab”may act an important role in the follow-up study in immunosenescence.

However, our present study also has some limitations. First, only English articles or reviews were selected from the WoSCC database, and some findings in other databases or written in different languages might have been missed. Second, because immunosenescence-related literature has increased dramatically in recent years, continuously updated material may be biased.

Fortunately, given the vast majority of data incorporated in our study, the conclusions would still be credible. Third, some information might be overlooked due to the inevitable differences and the reasonable systematic errors of CiteSpace and VOSviewer softwares.

5. Conclusion

In summary, the research into the function and mechanism of immunosenescence in diseases has important value and broad prospects. A total of 3875 publications on immunosenescence were searched. From annual number of publications, there was an explosive increase from 2020 to 2021. USA is the dominant country in this field. Pawelec G and his institution Univ Tubingen of GERMANY contributed the most articles. From cooperating network, the cooperation and exchange among different countries, institutions, and authors are still needed to deepen. The latest burst keywords were “gut microbiota”, “health”, “dysfunction” and “nivolumab”, indicating that present research on immunosenescence mainly focuses on its age-related changes, and its role in diseases, mechanisms, and potential interventions. We believe that our study may provide an important clue to the research of immunosenescence.

Author contribution statement

Chen HongBo and Hongbo Chen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Yiwei Luo: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper. Xiaohong Zhang, Ruzhen Luo and Yunlong Hou: Conceived and designed the experiments; Analyzed and interpreted the data. Yuhong Bian and Yanhui Liu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. Material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20362.

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