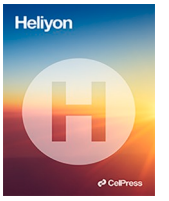
Heliyon 10 (2024) e24053

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

# Visual analysis of hotspots and trends in long COVID research based on bibliometric

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ARTICLE INFO

*Keywords:*
Long COVID
COVID-19
Bibliometric analysis
Research trends
Visual analysis
VOSviewer

ABSTRACT

After severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a series of symptoms may persist for a long time, which is now called long COVID. It was found that long COVID can affect all patients with COVID-19. Therefore, long COVID has become a hot topic. In this study, we used the WOS database as a sample data source to conduct a bibliometric and visual analysis of 1765 long COVID articles over the past three years through VOSviewer and R package. The results show that countries/authors in Europe and The United States of America contribute most of the articles, and their cooperation is also the most active. Keyword co-occurrence identified four clusters, with important topics including the mechanism, clinical symptoms, epidemiological characteristics, and management/treatment of long COVID. Themes such as "cognitive impairment", "endothelial dysfunction", "diagnosis", and "biomarkers" are likely to be the focus of new attention in the coming period. In addition, we put forward the possible research opportunities on long COVID for researchers and practitioners to facilitate future research.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) has spread across the world and caused morbidity and mortality at an unprecedented scale. As of April 6, 2023, according to data released by the World Health Organization (WHO), there have been 762 million confirmed cases of COVID-19 and more than 6.89 million deaths worldwide. As the COVID-19 continues and the number of recovered individuals increases, more and more evidences show that a higher proportion of COVID-19 patients may suffer series of symptoms across multiple organs and systems after the nucleic acid test came back negative [1,2], which commonly referred to as COVID-19's long-term symptoms or long COVID. In addition to long COVID, this condition is also named as post-acute COVID-19 syndrome, post COVID syndrome, COVID long hauler, post-acute sequelae of COVID-19, or post COVID condition [3]. To characterize this distinct condition, several health organizations provide interim definitions. American Centers for Disease Control and Prevention (CDC) uses the term "post-COVID status" (PCC) as an umbrella term for the widespread health consequences that may occur four or more weeks after being infected with SARS-CoV-2 [4]. The definition given by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) is one or more symptoms which persist or relapse/remit for more than 12 weeks after being diagnosed with COVID-19, and cannot be explained by other reasons [5]. And the National Institute for Health and Clinical Excellence (NICE) distinguishes between diseases (Ongoing symptomatic COVID-19, subacute infection period) that occur within 4–12 weeks after novel coronavirus infection

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https://doi.org/10.1016/j.heliyon.2024.e24053
Received 2 July 2023; Received in revised form 23 November 2023; Accepted 3 January 2024
Available online 6 January 2024

and symptoms that persist for more than 12 weeks (Post COVID-19 syndrome, new post-corona syndrome or chronic disease) [6]. What can be clarified is that long COVID is not a disease, but a condition.

Current studies have found that long COVID has the following characteristics: (1) Long COVID may occur regardless of gender, age, or the severity of the initial SARS-CoV-2 infection. An early study found that 87.4 % of patients recovering from acute novel coronavirus pneumonia had at least one symptom at follow-up 1 month after hospital discharge [7]. According to the CDC report, 20.8 % of young and middle-aged people aged 18–64 and 26.9 % of the elderly aged 65 and older developed sequelae associated with SARS-CoV-2 infection [8]. (2) Patients may have one or more long COVID symptoms at the same time. Some observational studies have reported persistent symptoms occurred in patients with long COVID, and at least 1/3 of patients have more than one symptom [9–13]. (3) Some long COVID patients have longer expected recovery time. A questionnaire study for multinational patients showed that more than 91 % of patients with long COVID had symptom recovery time exceeding 35 weeks, and over 80 % of patients had symptoms exceeding 6 months [14]. A study has also reported a long duration of COVID symptoms of 9 months in hospitalized patients while 4 months in non-hospitalized patients. It has also been suggested that the time of symptom resolution seems to depend on the risk factors before onset, the severity of the acute phase, and the symptoms experienced by the patients [15–17]. There are several reports that long COVID could affect more than 1 billion people worldwide in just a few years [18]. Thus, COVID-19 is not just an acute event, and the effects of long COVID on individual health or the public health burden cannot be ignored.

Bibliometric analysis provides a quantitative method to review and survey the existing literature in a particular field [19]. It has been widely used in various fields, including biomedical research [20–23]. Bibliometrics can provide researchers with key information, contribute to discovering frontiers, and help to evaluate countries or regions, authors, journals, and other information in specific fields through qualitative and quantitative analysis of publications. With the emphasis on long COVID, more and more relevant literature has been published [24,25], including a large number of systematic reviews and meta-analyses [26–28]. Most of the related literature have summarized the long COVID epidemiological characteristics, pathophysiology, risk factors and management. However, relatively few are about the objective, quantitative and comprehensive analysis of the literature related to long COVID [29,30]. This study provides a quantitative and visual overview of the information on long COVID in the literature through a comprehensive analysis of relevant articles published worldwide from 2021 to February 2023, and briefly describes the current status of long COVID research, aiming to predict the possible research trends in this field and provide guidance for future research directions and development.

## 2. Methods

### 2.1. Data collection and search strategies

Web of Science is one of the most important database platforms for accessing global academic information, covering multiple disciplines, and including many of the most influential academic journals. In addition, Web of Science includes only the most important academic journals in each discipline, which can meet the requirements of Bradford's law in bibliometrics. Therefore, some scholars think that Web of Science is the most suitable database for bibliometric analysis [31]. And the Science Citation Index Extension (SCIE) of the Web of Science Core Collection (WoSCC) was chosen as this search source because SCIE covers the most authoritative mainstream academic journals in the natural sciences.

To avoid deviations due to database updates, the literature search was conducted on March 19th, 2023. The search was conducted with the terms "COVID-19" and "long COVID" (synonyms extracted from MeSH in PubMed). Chosen publication time ranges from January 1st, 2020 to February 28th, 2023. Further detailed search strategy is provided in supplementary materials (S1). The screening criteria included that the literature type was limited to "article" and "review" and the language was limited to English publication. After screening, 1765 papers were obtained, including 1319 articles and 446 reviews (Fig. 1). To ensure the accuracy, two authors (Lai Zongqiang and Pu Tao) independently completed the search and confirmed the data. The study extracted all available information from the raw data to a plain text file.

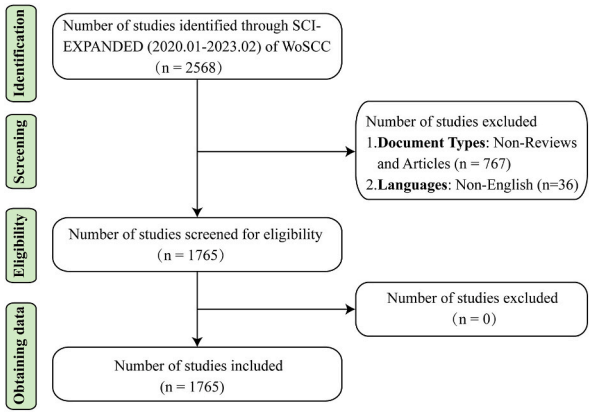


**Fig. 1.** Flow diagram of long COVID literature search and screening.

### 2.2. Data extraction and analysis

In this study, R package "bibliometrix" was used for bibliometric analysis [32]. Additionally, "biblioshiny", a shiny app providing a web-interface for bibliometric, was used for extracting variable data. We analyzed and visualized information such as publication trends, journals, author distribution, countries and institutions, collaborative networks, influence, most worldwide cited papers, and performed keywords clustering analysis. Journal impact factors (IF) and partition information refer to "2022 Journal Citation Reports".

VOSviewer (version 1.6.19) was also used for visualization of co-authors and keyword co-occurrence between countries/institutions/authors to promote understanding of the long COVID studies. In the resulting graph, the node represents countries/institutions/authors/keywords, the size of the nodes indicates the number of publications or the frequency of occurrence, the thickness of the curve represents the strength of the link, and different colors labels clusters.

## 3. Results

### 3.1. Global trends in long COVID publications

A total of 1765 publications that met the eligibility criteria were found and retrieved from WoSCC, and Fig. 2a shows the main information from the selected publications and indicates that long COVID is a new research field (mean age of the literature = 1.11 years). Fig. 2b shows the number of publications (Np) in long COVID from 2020 to 2023. The number of long COVID research papers was only 10 in 2020, but it has rapidly increased to 413 since 2021 and exceeded 1000 in 2022. As of February, 179 papers had also been published in 2023. In order to further predict the Np throughout 2023, we built a polynomial regression model using Microsoft Office Excel 2016. The time prediction curve model was successfully established through data fitting, and the formula $y = 185.61\ x^2$-$168.34\ x$ with a good fitting degree ($R^2 = 0.9998$) was obtained. Based on the fitted curve, we estimated that the Np will reach approximately 2300 in 2023. Similarly, by retrieving COVID-19-related papers, the proportion of long COVID research in COVID-19 research also increased rapidly (Fig. 2c), from 0.02 % in 2020 to 1.28 % in 2022. As of February, the proportion of research in 2023 had exceeded 2 %. These results indicate that with the progress of the COVID-19 pandemic, more and more sequelae of COVID-19 have emerged, and long COVID has attracted great attention.

### 3.2. Development trend of citations

The annual citations of papers related to long COVID exhibited dynamic changes and a gradually increasing trend (Fig. 2d). As shown in Table 1, those highly cited publications provided by Nalbandian A (2021), Sudre CH (2021), Lopez-Leon S (2021), Davis HE (2021) and Crook H (2021) made significant contributions to the field of long COVID.

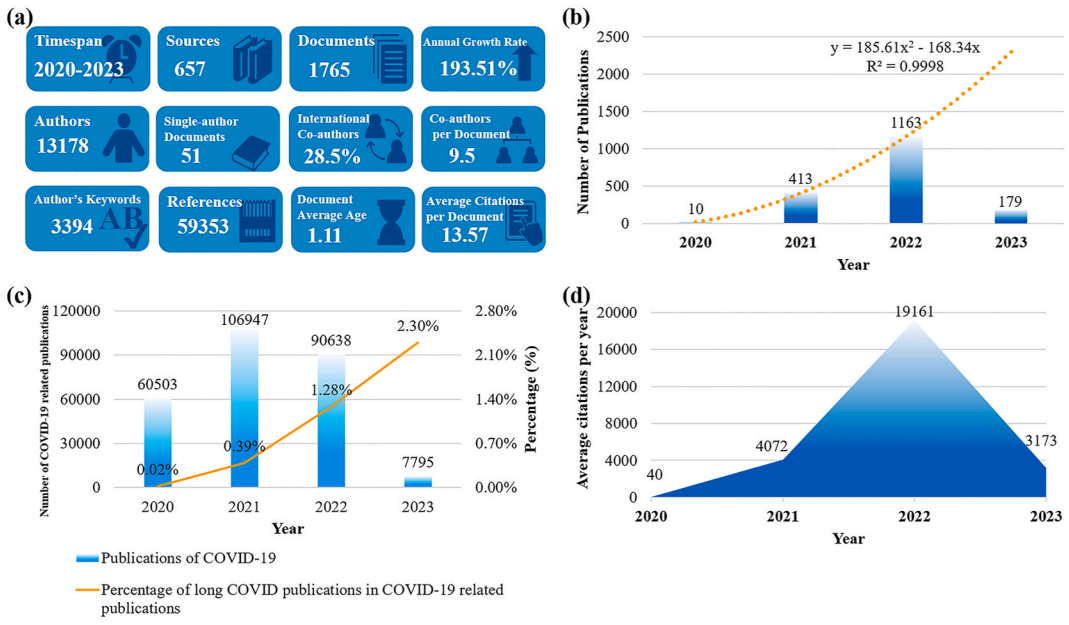


**Fig. 2.** (a) Main information of publications in long COVID. (b) Polynomial curve fitting of annual publications growth in long COVID. (c) Trends of the proportion of publications on long COVID in COVID-19-related research. (d) The number of citations per year in long COVID.

**Table 1**
Top 10 cited papers ranked by total citations in long COVID.

| Paper | DOI | TC | AC | Normalized TC |
|---|---|---|---|---|
| Nalbandian A, 2021, Nature Medicine | 10.1038/s41591-021-01283-z | 1469 | 489.67 | 33.83 |
| Sudre CH, 2021, Nature Medicine | 10.1038/s41591-021-01292-y | 736 | 245.33 | 16.95 |
| Lopez-Leon S, 2021, Scientific Reports | 10.1038/s41598-021-95565-8 | 693 | 231.00 | 15.96 |
| Davis HE, 2021, EClinicalMedicine | 10.1016/j.eclinm.2021.101019 | 636 | 212.00 | 14.65 |
| Crook H, 2021, British Medical Journal | 10.1136/bmj.n1648 | 380 | 126.67 | 8.75 |
| Mandal S, 2021, Thorax | 10.1136/thoraxjnl-2020-215818 | 358 | 119.33 | 8.24 |
| Soriano JB, 2022, The Lancet. Infectious Diseases | 10.1016/S1473-3099(21)00703-9 | 317 | 158.50 | 44.13 |
| Yong SJ, 2021, Infectious Diseases | 10.1080/23744235.2021.1924397 | 277 | 92.33 | 6.38 |
| Brodin P, 2021, Nature Medicine | 10.1038/s41591-020-01202-8 | 276 | 92.00 | 6.36 |
| Moreno-Pérez O, 2021, The Journal of Infection | 10.1016/j.jinf.2021.01.004 | 265 | 88.33 | 6.10 |

TC total citations, AC average citations per year.

### 3.3. Journal analysis

In total, 657 journals were involved in publishing these papers. Table 2 shows the top 10 most productive journals. Among them, *International Journal of Environmental Research and Public Health* was the most popular journal (n = 82, 4.65 %), followed by *Journal of Clinical Medicine* (n = 70, 3.97 %) and *Frontiers in Immunology* (n = 42, 2.38 %). It can be noted that these above journals are open-source journals, and although scholars still disagree on the best way to achieve open access, the concept of free sharing of research results is undoubtedly widely accepted, which also promotes the rapid development of open-source journals [33]. Fig. 3a depicts the Np per year by the top 10 journals in long COVID over the retrieval period. Fig. 3b shows the annual changes of cumulative Np published in the top 10 journals. The cumulative Np published in these journals was 376 (27.3 %), indicating that these journals pay great attention to long COVID. We further analyzed the total citations (TC) and H-indexes of journals in this study. Table 3 shows the top 10 most frequently cited journals, with *Nature Medicine* ranking first. *Journal of Clinical Medicine* had the highest H-index, followed by *Frontiers in Immunology* and *International Journal of Environmental Research and Public Health*, indicating that these journals are more influential in long COVID.

### 3.4. Author analysis

Through analyzing the author information, we can understand the representative scholars and core research strengths in this field. The dataset consists of 13,178 authors, with an average of 9.5 authors participating in each article. Table 4 lists the top 10 authors in the Np with their H-indexes, TCs, affiliations and countries. These authors were mainly from Spain, Italy, and the United Kingdom. Fernandez-de-las-Penas Cesar (Np = 30), Buonsenso Danilo (Np = 19) and Munblit Daniel (Np = 15) ranked the top 3 according to the Np. The author with the highest H-index (H = 11) and the most TC (TC = 636) was Munblit Daniel from Imperial College London of the United Kingdom, indicating that his outstanding contributions to the field of long COVID research.

Fig. 4a shows the changes of the Np over time for the top 10 authors, with most authors publishing relevant research papers since 2021. Analyzing the author collaboration network can provides insight into the distribution of academic groups in this research area, so we use VOSviewer to visualize the collaboration networks of core authors in long COVID. According to Lotka's Law, we positioned authors who had published 5 or more papers (including 5) as core authors, for a total of 83 core authors. As shown in Fig. 4b, these authors exhibited the characteristics of a small-scale cooperative network. And the authors of the formed cooperative network were mostly limited to the same region or country, indicating that the research teams in the field had not formed a global scale in the short time since the appearance of long COVID. After using Microsoft Charticulator website to further analyze the author collaboration network derived from VOSviewer, and obtaining the collaboration network knowledge graph of the most prolific 30 authors (Fig. 4c), we found that Greenhalgh Trisha from University of Oxford and Sivan Manoj from University of Leeds had relatively close collaboration.

**Table 2**
Top 10 journals with the most publications in long COVID.

| Rank | Journal | Np | IF (2022) | Partition (2022) | Countries |
|---|---|---|---|---|---|
| 1 | International Journal of Environmental Research and Public Health | 82 | 4.614 | Q2 | switzerland |
| 2 | Journal of Clinical Medicine | 70 | 4.964 | Q2 | USA |
| 3 | Frontiers in Immunology | 42 | 8.786 | Q1 | Switzerland |
| 4 | Frontiers in Medicine | 42 | 5.058 | Q2 | Switzerland |
| 5 | Viruses-Basel | 29 | 5.818 | Q2 | Switzerland |
| 6 | BMJ Open | 25 | 3.006 | Q2 | England |
| 7 | International Journal of Molecular Sciences | 25 | 6.208 | Q1 | USA |
| 8 | Scientific Reports | 22 | 4.996 | Q2 | England |
| 9 | PLoS One | 20 | 3.752 | Q2 | USA |
| 10 | Biomedicines | 19 | 4.757 | Q2 | Switzerland |

Np number of publications, IF impact factor.

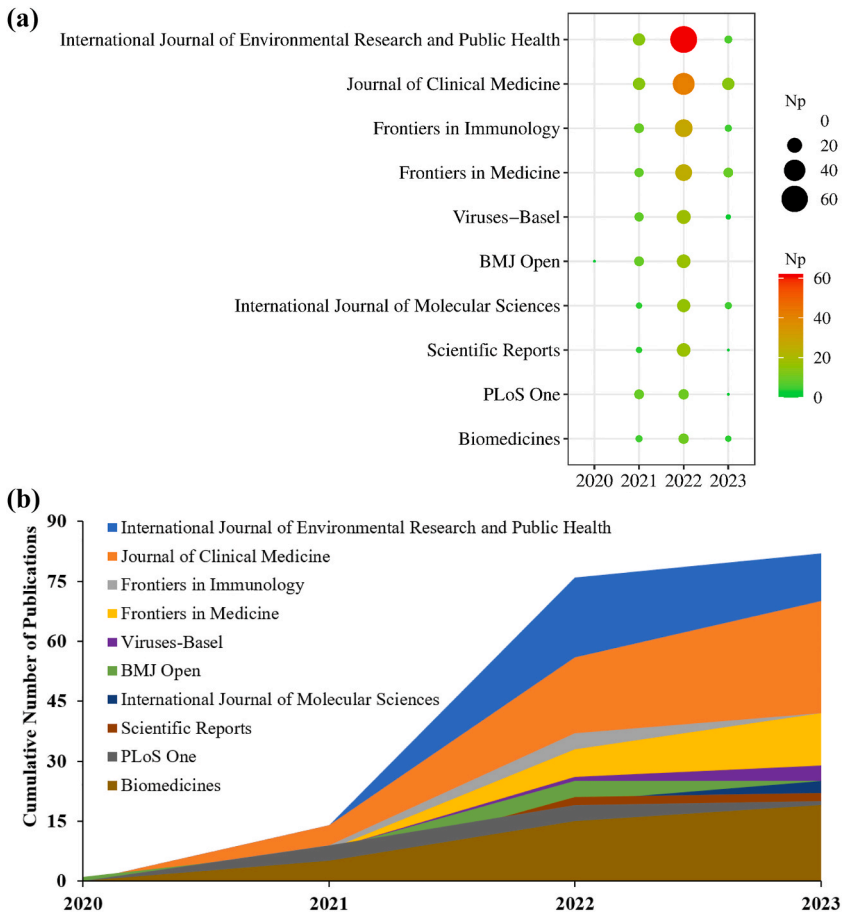


**Fig. 3.** (a) The annual publications of top 10 journals in long COVID. Size and color of the circle represents the number of publications. (b) The cumulative number of publications of top 10 journals in long COVID.

**Table 3**
Top 10 journals ranked by local impact in long COVID.

| Journals | TC | Journal | H-Index |
|---|---|---|---|
| Nature Medicine | 2909 | Journal of Clinical Medicine | 10 |
| eClinicalMedicine | 996 | Frontiers in Immunology | 9 |
| Scientific Reports | 924 | International Journal of Environmental Research and Public Health | 9 |
| International Journal of Environmental Research and Public Health | 528 | Nature Communications | 9 |
| BMJ-British Medical Journal | 471 | BMJ Open | 8 |
| The Lancet Infectious Diseases | 417 | Clinical Infectious Diseases | 8 |
| Journal of Clinical Medicine | 398 | Nature Medicine | 8 |
| Journal of Infection | 391 | Clinical Microbiology and Infection | 7 |
| Nature Communications | 372 | eClinicalMedicine | 7 |
| Acta Paediatrica | 370 | Frontiers in Medicine | 7 |

TC total citations.

### *3.5. Analysis of countries/regions and institutions*

To clarify which countries/regions have made the most outstanding contributions to long COVID, we analyzed the national contributions and found that these papers came from 93 countries (Fig. 5a). Table 5 lists the top 10 most productive countries. The top five countries were the United States of America (Np = 310, 17.56 %), the United Kingdom (Np = 222, 12.58 %), Italy (Np = 213, 12.07 %), Germany (Np = 114, 6.46 %), and Spain (Np = 81, 4.59 %), which occupied more than half of the total published papers (Np = 940, 53.25 %). Further analysis of the collaborative relationships between the top 10 countries revealed that 65 papers in the United States of America came from international cooperation, followed by 62 papers in the United Kingdom (Fig. 5b). Through the collaboration network, we also analyzed the national cooperation among the top 30 countries. As shown in Fig. 5c, the United Kingdom has closest

**Table 4**
Top 10 authors with the most publications in long COVID.

| Rank | Authors | Np | H-index | TC | Affiliations | Countries |
|---|---|---|---|---|---|---|
| 1 | Fernandez-De-Las-Penas Cesar | 30 | 6 | 273 | Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos | Spain |
| 2 | Buonsenso Danilo | 19 | 9 | 416 | Department of Woman & Child Health & Public Health, Fondazione Policlinico Universitario A Gemelli IRCCS | Italy |
| 3 | Munblit Daniel | 15 | 11 | 636 | Faculty of Medicine, Imperial College London | United Kingdom |
| 4 | Valentini Piero | 14 | 7 | 355 | Department of Woman & Child Health & Public Health, Fondazione Policlinico Universitario A Gemelli IRCCS | Italy |
| 5 | Arendt-Nielsen Lars | 13 | 4 | 99 | Faculty of Medicine, Aalborg University | Denmark |
| 6 | Sivan Manoj | 12 | 5 | 63 | Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds | United Kingdom |
| 7 | De Rose Cristina | 11 | 5 | 340 | Department of Woman & Child Health & Public Health, Fondazione Policlinico Universitario A Gemelli IRCCS | Italy |
| 8 | Pellicer-Valero Oscar J | 11 | 4 | 102 | Engineering School, Universitat de València | Spain |
| 9 | Greenhalgh Trisha | 10 | 6 | 273 | Department of Primary Care Health Sciences, University of Oxford | United Kingdom |
| 10 | Martin-Guerrero Jose D. | 10 | 4 | 102 | Engineering School, Universitat de València | Spain |

Np number of publications, TC total citations.

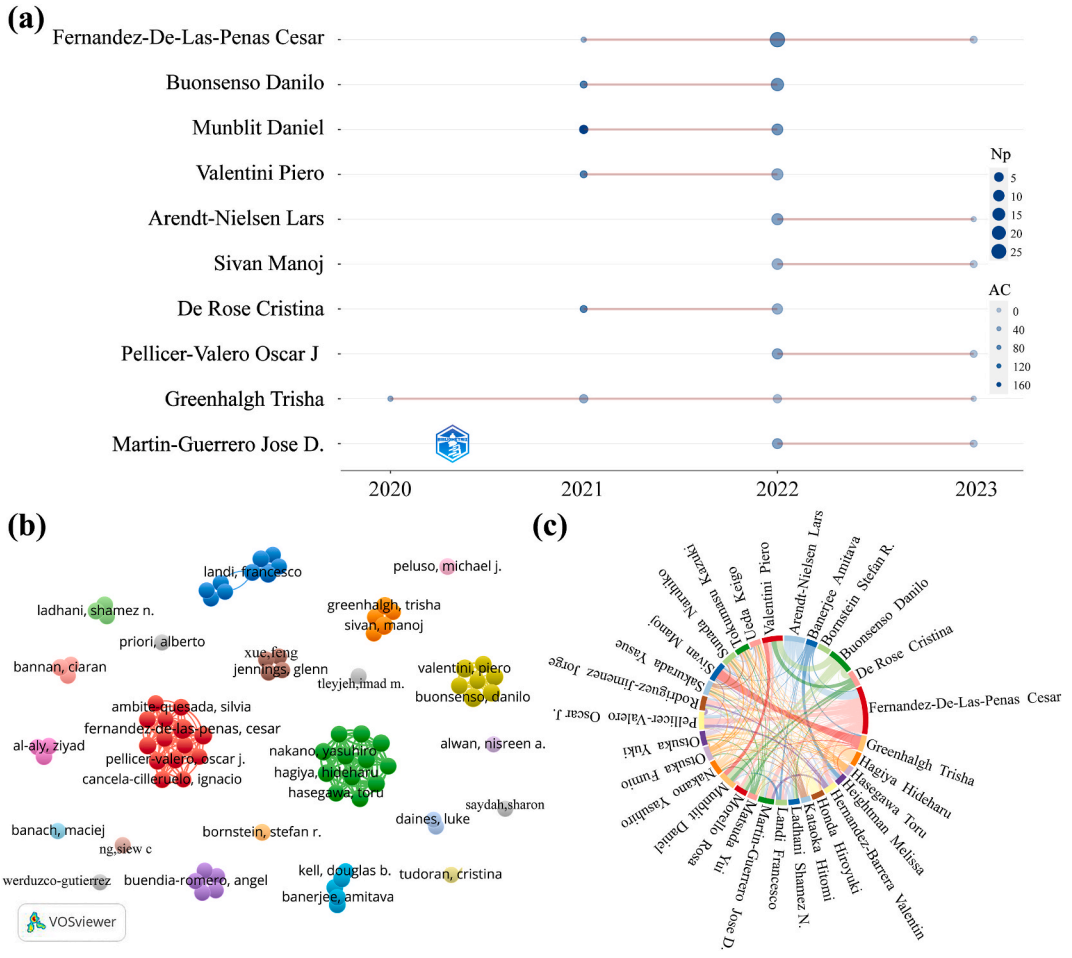


**Fig. 4.** (a) The annual publication of top 10 authors over time in long COVID. Size of the circle represents the Np. Depth of the circle represents the average annual citation. (b) Author collaboration network knowledge graph in long COVID. (c) The collaboration network knowledge graph of top 30 publication authors in long COVID.

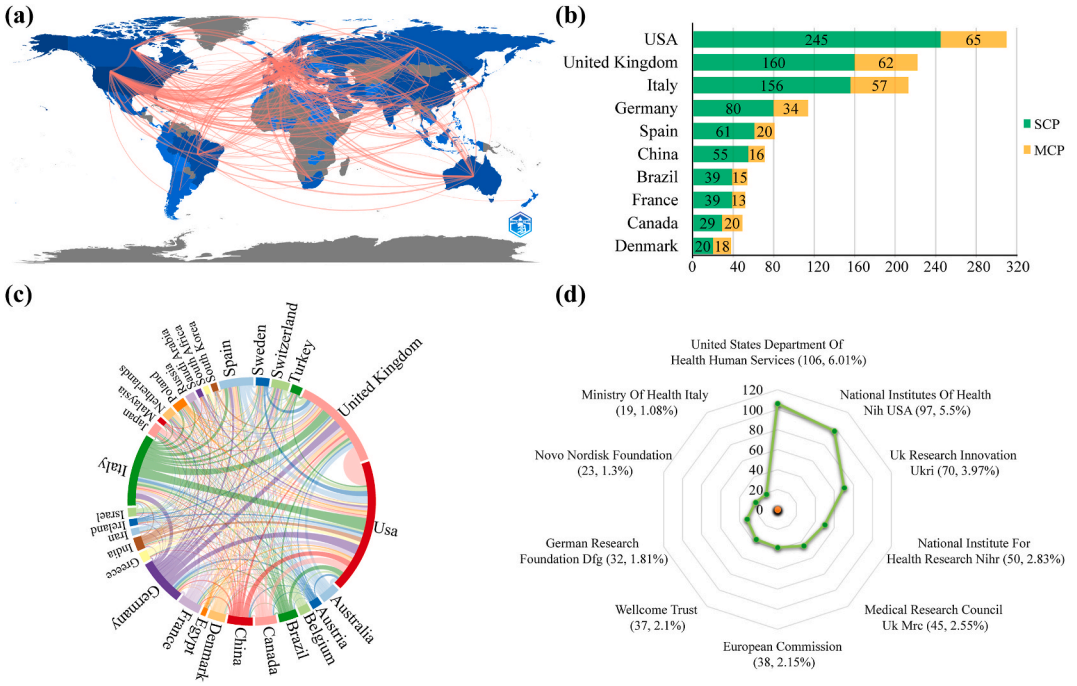


**Fig. 5.** (a) Global distribution of publications in long COVID. Color represents Np. Line represents the cooperative relationship between countries. (b) The papers partnerships of top 10 countries in long COVID. (c) The collaboration network of top 30 countries in long COVID. (d) The top 10 related funding agencies for the support in long COVID research.

**Table 5**
Top 10 countries/regions and affiliations involved with the most publications in long COVID.

| Rank | Countries | Np | TC | AC | Affiliation | Np |
|---|---|---|---|---|---|---|
| 1 | USA | 310 | 6540 | 21.10 | Imperial College London (United Kingdom) | 93 |
| 2 | United Kingdom | 222 | 5560 | 25.00 | Univ Sao Paulo (Brazil) | 75 |
| 3 | Italy | 213 | 2083 | 9.80 | Univ Oxford (United Kingdom) | 71 |
| 4 | Germany | 114 | 1082 | 9.50 | Harvard Medical School (USA) | 64 |
| 5 | Spain | 81 | 1238 | 15.30 | King's College London (United Kingdom) | 60 |
| 6 | China | 71 | 415 | 5.80 | Univ Cattolica del Sacro Cuore (Italy) | 55 |
| 7 | Brazil | 54 | 223 | 4.10 | Univ Milan (Italy) | 53 |
| 8 | France | 52 | 429 | 8.80 | Johns Hopkins Univ (USA) | 49 |
| 9 | Canada | 49 | 660 | 12.70 | Copenhagen Univ Hospital (Denmark) | 48 |
| 10 | Denmark | 38 | 690 | 18.20 | Geneva Univ Hospitals (Switzerland) | 47 |

Np number of publications, TC total citations, AC average citations per year.

cooperation with United States of America, while Italy with the United Kingdom and the United States. More than 3400 institutions were active in long COVID, and Table 5 shows the top 10 most productive institutions. Imperial College London, Univ Sao Paulo, and Univ Oxford were among the top three. The top 10 institutions are distributed in the following countries: three in the United Kingdom, two in the United States of America, two in Italy, and one in Brazil, Denmark, and Switzerland, respectively. Fig. 5d depicts the major funding agencies, mostly from the United Kingdom and the United States of America, indicating strong support for long COVID research in both countries.

### *3.6. Keyword analysis*

#### *3.6.1. Analysis of high-frequency keywords in long COVID*

Keywords are summarization or core information of research contents, and high-frequency keywords often represent the research focus in the field. In this study, we used VOSviewer to analyze the keyword information and perform the visualization of keyword co-occurrence analysis based on the frequency, aiming at pointing out the research hotspots and topics in long COVID. In total, 5682 keywords were extracted from the papers, including 3394 author's keywords and 2288 keywords plus. The top 50 keywords (excluding search terms) that occur frequently in keywords plus and author's keywords are represented in the wordcloud by R package Bibliometrix. In the keywords plus, the most active keywords were "infection", "disease", "outcomes", "survivors", "depression",

"inflammation", "health", and "management" (Fig. 6a). Among the author's keywords, the most frequent keywords were "fatigue", "quality of life", "depression", "inflammation", "rehabilitation", and "children" (Fig. 6b).

All keywords (excluding search terms) in the literature were analyzed using VOSviewer, and those with a frequency of no less than 15 times were selected for visualization. As shown in Fig. 6c, a total of 102 keywords were identified. Those can be divided into four clusters according to the total link strength between keywords, which were distinguished with different colors.

Cluster 1 (red, 34 items) focused on mechanistic studies in long COVID. The pathogenesis of long COVID is not yet clear, and may be the result of multiple mechanisms. The mechanisms include immune imbalance (which can lead to reactivation of potential pathogens, including herpes viruses such as EBV and HHV-6) [34,35], dysbacteriosis including viral persistence [36–38], autoimmune responses initiated due to the similarity of pathogens and autologous molecules [39,40], abnormal microvascular coagulation and endothelial dysfunction [41], and abnormal neural signal transduction (including signal dysfunction in the brainstem and/or vagus nerve) [42,43]. An important paper published in Nature Review Microbiology reviewed the problem of long COVID, and elaborated on the possible mechanisms of various long COVID symptoms or organ disorders [44]. Based on the current evidence, the mechanisms of different symptoms in multiple organs involved in long COVID are distinctive and still need to be explored.

Cluster 2 (green, 26 items) was dominant by the multi-organ effects and clinical symptoms of long COVID. The symptoms of long COVID include a series of damages to various organs and systems such as the respiratory system, cardiovascular system, nervous system, endocrine system, urinary system, and immune system [45], which were also divided into physical symptoms and psychological/cognitive symptoms. A study covering 100 discharged patients with COVID-19 demonstrated that 24 % had post-traumatic stress disorder (PTSD), 18 % had new or aggravated memory problems, and 1 % had new or aggravated attention problems [46]. Other studies have shown that nearly half of COVID-19 survivors suffered a decrease in quality of life [7], 22 % had anxiety/depression [47], and 23 % had persistent psychological symptoms at 3 months [48]. Another study reported that among survivors in intensive care unit (ICU), 23 % had anxiety, 18 % had depression, and 7 % had post-traumatic symptoms [49]. Furthermore, patients with long COVID often had more than one symptom and the time of symptom resolution may be related to the risk factors before onset, the severity of

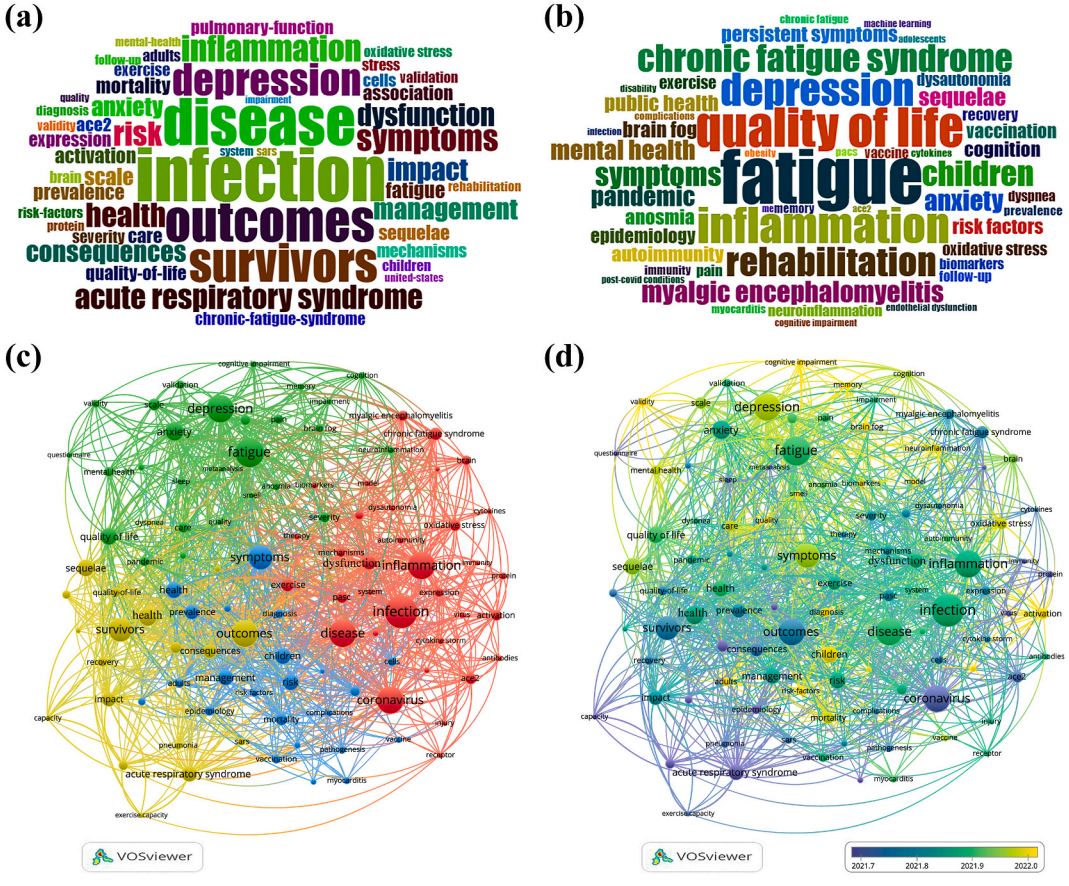


**Fig. 6.** (a) Cloud map of top 50 Author keywords in long COVID distribution. (b) Cloud map of top 50 Keywords Plus in long COVID distribution. (c) Cluster analysis of high-frequency keywords (frequency ≥15) based on all keywords of publications in long COVID. Different colors represent different clusters, the size of the circle represents the frequency the keywords appear, and the thickness of the line represents the total link strength between keywords. (d) Trends in keywords (frequency ≥15) over time based on all keywords of publications in long COVID. The blue represents the earliest keywords and the yellow represent the latest keywords.

the acute phase, and the symptoms of patients [50,51]. Current data showed significant differences in symptom resolution times of long COVID patients, such as 9 months in hospitalized patients and 4 months in non-hospitalized patients, and 15 % of subjects still had symptoms after 1 year, but the variation was large (95 % confidence interval, 10.3 %–21.1 %) [2].

Cluster 3 (blue, 23 items) was primarily associated with the epidemiological study of long COVID. The reported incidence of long COVID varies between different countries. Nevertheless, the UK Office for National Statistics (ONS) showed that the 5-week prevalence of any symptoms of long COVID in SARS-CoV-2-positive patients from April 22 to December 14, 2020 was 22.1 %, while the 12-week prevalence was 9.9 % [52]. A meta-analysis covering 54 studies and 2 medical history databases in 22 countries demonstrated that the 3-month incidence of long COVID was 6.2 % in patients with symptomatic COVID-19 from March 2020 to January 2022 [2]. In summary, the risk factors of long COVID can be divided into two categories, pre-infection factors (such as age, gender, previous comorbidities, and previous health status) and infection-related factors (such as disease severity, symptoms, viral load, hospital stay, and admission to ICU). There is no consensus on risk factors of long COVID. Some studies suggested that advanced age, female, white race, poor health prior to the epidemic, obesity, and asthma were correlated with severe long COVID symptoms [53]. A systematic literature review and meta-analysis investigated the risk factors related to SARS-CoV-2 infection, and concluded that female and previous complications might be the potential factors leading to long COVID. However, there was a moderate to high risk of bias in the elderly factor, which still requires further study [54]. Another study published in *Nature Medicine* revealed that in a cohort of patients with SARS-CoV-2 infection, risk factors of long COVID included female, minority, poverty, smoking, obesity, and various complications [55].

Cluster 4 (yellow, 19 items) was mainly related to the treatment and management research of long COVID. Due to the lack of systematic treatment for long COVID, most measures are mainly applied to improve clinical symptoms and prognosis, which includes the adoption of vaccines, individualized assessment and treatment, dietary supplements, and other potential therapies. Although guidelines have been published for the treatment/management of long COVID or incorporated relevant elements [6,56–58], they rarely address details of the treatment/management. Therefore, although some evidence-based therapies have not yet reached a consensus, they may contribute to the individualized treatment of long COVID. An Italian study showed that supplementation of L-arginine and vitamin C has beneficial effects on long COVID patients to attenuate their typical symptoms and improve their perception [59]. And another study found that inspiratory muscle training (IMT) could promote recovery from long COVID [60]. The use of small-molecule blockers to inhibit the inflammatory responses in COVID-19 is also a potential therapy, and one study has shown that Leronlimab (a monoclonal antibody that blocks CCL-5 function) could reduce interleukin-6 levels in the plasma of COVID-19 patients [61].

#### *3.6.2. Analysis of development trend of high frequency keywords in long COVID*

This study also predicted the future research trends of long COVID through the visual analysis by VOSviewer. As shown in Fig. 6d, VOSviewer assigned different colors to keywords according to the average year and frequency of appearance in publications, where blue represents the earlier appearing keywords, and yellow represents the newer (suggesting possible future research directions). The main keywords in the yellow nodes included "cognitive import", "brain fog", "endothelial dysfunction", "activation", "neuroinflammation", "children", "diagnosis", and "biomarkers". It can also be seen that the development dynamics of the four clusters were relatively unbalanced, with more yellow nodes in cluster 2.

### *3.7. Analysis of most cited papers in long COVID*

Highly cited papers refer to articles with great academic value and professional influence, and are one of the most important

**Table 6**
Top 10 cited original articles in long COVID.

| Rank | Title | First author | Year | Journal | IF | Partition | TC |
|---|---|---|---|---|---|---|---|
| 1 | Attributes and predictors of long COVID | Sudre CH | 2021 | Nature medicine | 87.241 | Q1 | 736 |
| 2 | Characterizing long COVID in an international cohort: 7 months of symptoms and their impact | Davis HE | 2021 | EClinicalMedicine | 17.033 | Q1 | 636 |
| 3 | 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalization for COVID-19 | Mandal S | 2021 | Thorax | 9.102 | Q1 | 358 |
| 4 | Immune determinants of COVID-19 disease presentation and severity | Brodin P | 2021 | Nature medicine | 87.241 | Q1 | 276 |
| 5 | Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study | Moreno-Pérez O | 2021 | The Journal of infection | 38.637 | Q1 | 265 |
| 6 | Preliminary evidence on long COVID in children | Buonsenso D | 2021 | Acta paediatrica | 4.056 | Q1 | 232 |
| 7 | Long COVID in a prospective cohort of home-isolated patients | Blomberg B | 2021 | Nature medicine | 87.241 | Q1 | 228 |
| 8 | How and why patients made Long Covid | Callard F | 2021 | Social science & medicine | 5.379 | Q1 | 227 |
| 9 | Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19 | Taquet M | 2021 | PLoS medicine | 11.613 | Q2 | 213 |
| 10 | Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study | Dennis A | 2021 | Clinical medicine | 5.41 | Q3 | 203 |

IF impact factor, TC total citations.

indicators for bibliometric analysis. The 10 most cited papers in original research and reviews worldwide are listed in Tables 6 and 7, respectively.

### 3.7.1. Top 10 original papers in long COVID

The top 10 most cited original papers were all published in 2021, and mainly reported in Q1 journals. Among them, *Nature Medicine* contributed three highly cited original works. This study provides a quick overview of the original long COVID studies by summarizing these 10 articles. In the initial stage of proposing the concept of long COVID, Felicity Callard published an article to trace the emergence of long COVID and the process of dissemination of this term [62]. Epidemiology involves collections, analyses, and predictions of disease-related information and can provide a scientific basis for disease prevention and control. Therefore, epidemiological studies of long COVID are very important, and several highly cited original papers have focused on this. Hannah E. Davis et al. conducted the first study to quantify the symptom trace of individual long COVID over a long period of time. They analyzed the symptoms of 3762 patients with confirmed or suspected novel coronavirus infection from 56 countries/regions, and estimated the prevalence of 203 symptoms in 10 organ systems [14]. A study led by British scientists analyzed long COVID events in 4182 patients with COVID-19 and found that the incidence of long COVID symptom duration was different. It also established a prediction model characterized by the number of symptoms in the first week, age and gender to identify the risk of long COVID [63]. In contrast, a study that analyzed electronic health record data from 273,618 patients with COVID-19 found that more than 1/3 of patients had one or more common long COVID symptoms between 3 and 6 months after the diagnosis of COVID-19 [51]. Danilo Buonsenso performed an assessment of persistent symptoms in children aged no more than 18 with COVID-19 and presented preliminary evidences for long COVID in children [64]. Some other literature focused on the risk factors of long COVID. Swapna Mandal found that blood biomarkers (d-dimer and C reactive protein) and chest X-ray imaging were meaningful examinations for early detection of long COVID through follow-up of persistent symptoms after hospitalization with COVID-19 [65]. A prospective cohort study concluded that long COVID symptoms were independently associated with the severity of the initial illness, increased antibody titers at recovery time, and pre-existing chronic lung disease [51]. Oscar Moreno-Pérez specifically evaluated the risk factors for long COVID and concluded that there were no baseline clinical features that could be used as an independent predictor of long COVID [66]. Petter Brodin discussed the impact of immunological factors on disease presentation and severity in COVID-19 and concluded that clinical outcomes, including long COVID, were associated with differences in immune system between age and sex [67]. And a prospective, community-based study in the United Kingdom found that 70 % of individuals at low risk of COVID-19 mortality had impairment in one or more organs 4 months after initial COVID-19 symptoms [68].

### 3.7.2. Top 10 review papers

A review can reflect the background, current research status, and development trend of a career, thus helping people to understand the latest research development of their concerned topic in a relatively short time. Several review articles outlined the epidemiological characteristics of long COVID [69–71], with the common clinical symptoms including weakness, general malaise, fatigue, anxiety, headache, cough, chest pain, odor change, taste change, diarrhea, and so on. The incidence reported varied from country to country. A paper summarizes the symptoms of long COVID in children [72]. Several review articles have discussed the pathophysiology, risk factors, and therapeutic/management of long COVID [73,74], while Ani Nalbandian reviewed the pathophysiology of long COVID and its organ-specific sequelae, and discussed the multidisciplinary management of survivors of COVID-19 [75]. Melanie Dani described a

**Table 7**
Top 10 cited reviews in long COVID.

| Rank | Title | First author | Year | Journals | IF | Partition | TC |
|---|---|---|---|---|---|---|---|
| 1 | Post-acute COVID-19 syndrome | Nalbandian A | 2021 | Nature medicine | 87.241 | Q1 | 1469 |
| 2 | More than 50 long-term effects of COVID-19: a systematic review and meta-analysis | Lopez-Leon S | 2021 | Scientific reports | 5.019 | Q1 | 693 |
| 3 | Long covid-mechanisms, risk factors, and management | Crook H | 2021 | BMJ-British Medical Journal | 93.333 | Q1 | 380 |
| 4 | A clinical case definition of post-COVID-19 condition by a Delphi consensus | Soriano JB | 2022 | Lancet Infectious diseases | 71.421 | Q1 | 317 |
| 5 | Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments | Yong SJ | 2021 | Infectious diseases | 5.838 | Q2 | 277 |
| 6 | Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms | Proal AD | 2021 | Frontiers in microbiology | 6.064 | Q1 | 187 |
| 7 | Characterising long COVID: a living systematic review | Michelen M | 2021 | BMJ global health | 8.056 | Q1 | 179 |
| 8 | Symptoms, complications and management of long COVID: a review | Aiyegbusi OL | 2021 | Journal of the Royal Society of Medicine | 18 | Q1 | 152 |
| 9 | Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19 | Ludvigsson JF | 2021 | Acta paediatrica | 4.056 | Q1 | 138 |
| 10 | Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis | Ceban F | 2022 | Brain, behavior, and immunity | 19.227 | Q1 | 135 |

IF impact factor, TC total citations.

series of clinical cases with long COVID symptoms and considered that the virus or immune-mediated disruption of the autonomous nervous system might cause orthostatic intolerance syndromes, and presented their rational for an underappreciated damaged autonomous physiology in long COVID, and put forward seven management methods including patient education and drug treatment [76]. And one paper used Delphi consensus to create a final consensus definition for long COVID in adults [77].

### 3.7.3. High cited original papers published in high-IF journals

Most of the highly cited papers were published in high-IF journals and dominated by original research. Some recently published articles may have a citation disadvantage due to length-time effect bias and thus may be overlooked. Therefore, we ranked the long COVID original research articles published in high-IF journals since 2022 according to TC (Supplementary material S2) and briefly described them. A total of 20 articles were extracted from 15 high-IF journals, with the average IF of 67.89. Among them, *Nature Medicine*, *Lancet Respiratory Medicine*, *Science*, *BMJ-British Medical Journal*, and *Lancet Child & Adolescent Health* each published two articles. Some of these articles continued to focus on the epidemiological characteristics of long COVID [78–81], and some have concentrated on long COVID in children and adolescents [82–84]. There are also articles focusing on the interaction of long COVID with other diseases or disease states, including diabetes [85] and cardiovascular disease [86,87]. And several articles specifically aimed at exploring certain specific effects of long COVID on people, such as mental health [88], smell and taste dysfunction [89], fatigue, cognitive, and respiratory symptom clusters [2]. Four articles studied the relationship between long COVID and immunity [90–93], and another article studied gut microbiota dynamics in patients with long COVID, suggesting that gut microbiota changes may affect the susceptibility to long COVID [94]. These papers were all published in 2022, which may reflect the research hotspots in recent periods.

### 3.7.4. Updated papers published in 2023

During the submission process, we also update the latest research, and conducted a search on November 22 (search time range from January 1, 2023 to October 31, 2023), and obtained 48 highly cited papers (supplementary material 3), hoping to enable readers to understand the latest research progress of long COVID. Table 8 shows 10 articles published in high impact factor journals. Among them, three are review articles. At the beginning of 2023, Nature Reviews Microbiology published a review of long COVID considers current diagnostic and treatment options are insufficient, and clinical trials must be prioritized that address leading hypotheses [1]. Another review summarizes the progress with COVID-19/long COVID drug discovery, and discusses the lessons learned about aspects such as drug repurposing, disease models and clinical development strategies [95]. And Professor Fedorowski et al. have reviewed the latest progress of cardiovascular autonomic dysfunction and postural tachycardia syndrome after long COVID [96]. People now have a new understanding of long COVID. A prospective cohort study puts forward the view that the definition developed of long COVID should be based on symptoms [97]. And in a cohort study, it is found that more severe acute illness and being unvaccinated were associated with a higher risk of reporting COVID-19 symptoms lasting 28 days or more [98]. Moreover, chronic viral infections (such as EBV, CMV, and HIV) may also have different effects on the development of long COVID [99]. These sound frightening, but some studies have found that most patients of long COVID with Mild COVID-19 are resolved within a year [100]. And in terms of treatment on COVID-19, the clinical significance of nirmatrelvir has been further confirmed, a cohort study found that treatment with nirmatrelvir can reduce the risk of long COVID [101]. Many researchers have also worked on how to predict long COVID. It has been found that circulating anti-nuclear autoantibodies in COVID-19 patients predict long COVID symptoms, indicating the role of autoimmunity in long COVID [102]. Ruffieux, H et al. established an online tool, which may capture recovery from SARS-CoV-2 infection or long COVID

**Table 8**
The updated papers published in 2023 to long COVID.

| Title | DOI | Journals | IF | TC |
|---|---|---|---|---|
| Long COVID: major findings, mechanisms and recommendations | 10.1038/s41579-022-00846-2 | Nature Reviews Microbiology | 78.297 | 375 |
| Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study | 10.1136/bmj-2022-072529 | British Medical Journal | 93.333 | 52 |
| Chronic viral coinfections differentially affect the likelihood of developing long COVID | 10.1172/JCI163669 | Journal of Clinical Investigation | 19.456 | 41 |
| Circulating anti-nuclear autoantibodies in COVID-19 survivors predict long COVID symptoms | 10.1183/13993003.00970–2022 | European Respiratory Journal | 33.795 | 40 |
| Association of Treatment With Nirmatrelvir and the Risk of Post-COVID-19 Condition | 10.1001/jamainternmed.2023.0743 | Jama Internal Medicine | 44.409 | 37 |
| Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection | 10.1001/jama.2023.8823 | JAMA | 157.335 | 34 |
| Therapeutic strategies for COVID-19: progress and lessons learned | 10.1038/s41573-023-00672-y | Nature Reviews Drug Discovery | 112.288 | 32 |
| Persistent COVID-19 Symptoms at 6 Months After Onset and the Role of Vaccination Before or After SARS-CoV-2 Infection | 10.1001/jamanetworkopen.2022.51360 | JAMA Network Open | 13.353 | 11 |
| Autonomic dysfunction and postural orthostatic tachycardia syndrome in post-acute COVID-19 syndrome | 10.1038/s41569-023-00842-w | Nature Reviews Cardiology | 49.421 | 8 |
| A patient-centric modeling framework captures recovery from SARS-CoV-2 infection | 10.1038/s41590-022-01380-2 | Nature Immunology | 31.250 | 8 |

IF impact factor, TC total citations.

based on ' systemic recovery ' profiles data [103].

## 4. Discussion

Long COVID has arguably become a common disease with significant impact on both individuals and the whole society. The heightened international interest in long COVID has also contributed to an accelerated pace of diagnosis and treatment options for the hard-to-attribute disease following a SARS-CoV-2 infection. For human survivors of the global epidemic, all that can be done is to improve the understanding of long COVID based on scientific research so that the damage of the epidemic is minimized and the next outbreak can be adequately faced. For these reasons, this study provides a bibliometric analysis of long COVID studies intending to enable stakeholders to quickly understand the current status of long COVID.

### 4.1. Literature characteristics

Long COVID was first reported in an article published by *BMJ Opinion* on May 5th, 2020, in which Paul Garner, a professor of infectious diseases, shared his emergence of constantly tired and dizzy 7 weeks after COVID-19 [104]. This article generated a lot of interest in the community. After this, more and more people shared their experiences with the new crown on the internet, and the term "long COVID" became popular and was gradually recognized and taken seriously by the academic community. By 2021, the research papers on long COVID have proliferated.

Based on the analysis of the periodicals published, it was found that *International Journal of Environmental Research and Public Health*, *Journal of Clinical Medicine*, and *Frontiers in Immunology* had the most published papers. The top 10 journals with the highest Np all supported open access, allowing research results to be published quickly and disseminated worldwide rapidly, which may account for the larger number of long COVID articles published in these journals. In addition, to judge the quality of a journal, it is necessary to comprehensively evaluate its TC and H-index. *Nature Medicine* had the most TC and contributed three highly cited original papers and one highly cited review, demonstrating its leading position in long COVID research. And *Journal of Clinical Medicine* had the highest H-index, followed by *Frontiers in Immunology*.

In order to identify which countries/regions have a prominent position in long COVID research, we analyzed country contributions. The results showed that these papers were mainly from advanced developed countries in European and American areas, the top 5 countries with the most Np were the United States of America, the United Kingdom, Italy, Germany, and Spain, which account for more than half of the total number of publications (53.25 %), and the analysis of national collaboration networks also suggested that these countries were at the core of the global collaboration. Almost all the top 10 research institutions in terms of publication volume were also located in Europe and the United States of America. Further synthesizing the results of the author and country collaboration networks, long COVID has received attention and research in most regions/countries around the world, but the data is still blank in some low and middle-income areas such as Africa (Fig. 5a). The authors continued to pay attention to long COVID research, and found that an editorial in *The Lancet* in March 2023 pointed out that at least 65 million people were currently battling with long COVID [105]. Long COVID has become a global problem that requires a globally coordinated multidisciplinary research agenda that brings together governments, non-governmental organizations, and civil societies. But at present, only a few countries around the world have formed special institutions and allocations for long COVID. For example, the United States of America has developed a national research action plan on long COVID and allocated $ 1.15 billion for the "Research COVID to Enhance Recovery, RECOVER" project [106].

### 4.2. Research hotspots of long COVID

By analyzing information elements such as high-frequency keywords, keyword clustering, and highly cited papers, our study finds that the research hotspots in long COVID are mainly focused on four areas: (1) The mechanism studies of long COVID. The mechanism of long COVID were complex, and its symptoms can manifest in multiple organ systems. Yet the current mechanism is often only explained for certain specific symptoms. However, there is no doubt that the coexisting systemic impairment and autoimmune responses play an important role in long COVID. It has been suggested that inflammation may be key to the pathogenesis of long COVID [107], and one study found that inflammatory markers can remain elevated for months in patients with long COVID [90]. In all, the immune system can affect other systems through a variety of physiological pathways, however, the specific mechanisms remain to be further investigated. Some interesting studies have also suggested that the mechanism of the development of long COVID may be related to human gut microbes [108], one of which recruited 106 patients with COVID-19 and found two distinct bacterial clusters in patients presenting with symptoms of long COVID compared with those without symptoms, and the gut bacterial composition of patients with long COVID on admission was enriched for 19 species of bacteria and characterized by Bifidobacterium, Blautia and Bacteroides [94]. (2) Clinical symptom studies of long COVID. Currently, the determination of long COVID often relies on the symptoms that appear after SARS-CoV-2 infection; therefore, the identification of specific clinical symptoms is also of positive significance for the diagnosis of long COVID. However, diagnosis of long COVID from a symptomatic perspective is also difficult because these symptoms (e.g., fatigue, headache, musculoskeletal pain, etc.) are also common in the general population. (3) The epidemiological characteristics studies of long COVID. The epidemiology of long COVID has been investigated in most parts of the world, and its prevalence varies from country to country, influenced by the length of the follow-up period, the population assessed, and the accuracy of self-reporting. Studies have also focused on identifying risk factors for long COVID, because identifying individuals at risk can guide medical management plans and reshape medical regimens accordingly. In a study released by *Cell*, researchers identified several factors that can predict whether patients are likely to develop long COVID at the beginning of COVID-19 diagnosis, including

antibodies, type 2 diabetes, SARS-CoV-2 RNA levels in the blood, and EBV DNA levels [109]. It has also been found that the pre-existence of asthma is significantly associated with long COVID [63]. In addition to this, the previously described risk factors include advanced age, female, and obesity, but remain open to debate. (4) Therapy/management studies for long COVID. As mentioned above, there are many long COVID-related guidelines available, but the details of treatment and drug recommendations are lacking. Since the epidemic, the field of vaccine and drug development for COVID-19 has been booming, with star products like Paxlovid and Molnupiravir, while marketed drugs or therapies for the treatment of long COVID remain elusive. It is because the unidentified mechanism of long COVID makes the development of therapeutic drugs difficult and full of uncertainty. Therefore, the long COVID therapy may still needs a long wait [110]. Despite this, attempts to find effective treatments and drugs have continued. This study searched the global clinical trials platform (https://clinicaltrials.gov/), and found that there are currently 406 clinical trials registered for long COVID as of April 11, 2023, including 209 studies of clinical trials.

### *4.3. Possible research directions*

With the possibility of viral mutations, the epidemiology, risk factors, pathogenesis, and therapeutic management of long COVID remain pressing issues and will become a hot topic for future research. In addition, this study also suggested some possible research directions for further exploration. (1) The impact of different novel coronavirus variants on long COVID needs to be further explored, compared, and summarized. (2) Long COVID in asymptomatic and mildly infected patients is easily overlooked, and the characteristics of this group also need to be explored. (3) There may be mutual influence between different symptoms of long COVID, and the relationship between different organs/symptoms should be further investigated. (4) Recent studies have found that the genomic structure of human cells may change after infection with SARS-CoV-2, and this effect may be associated with long COVID [111]. Therefore, long COVID should be intensively studied at the genetic level. (5) With the explosion and application of advanced technologies such as artificial intelligence (AI), deep sequencing, and machine learning, people should promote the application of these technologies in long COVID.

### *4.4. Limitations*

This study still has some limitations. First, our study inevitably omitted some relevant literature due to the limitations of the search database and language. The choice of document types was restricted to articles and reviews because these are the most common forms of publications, and we also searched for other document types (for example, news and conference abstracts) and found them to be smaller in number and less frequently cited. Second, the continuous updating of the literature database will lead to the problem of timeliness in this study. Even through the same search terms, searching at different periods will gain different results, and the latest progress in the field needs to be updated continuously. This study only analyzed published papers, and some of the most recent publications may have been missed by us. As the long COVID studies continues to develop, more publications will become available for analysis. Third, all current bibliometric analysis tools can currently only extract specific information from publications for analysis, and some potentially useful information may be missed. To remedy this deficiency, this study interpreted the research content of highly cited papers to provide a more comprehensive analysis of the current research state in long COVID.

## 5. Conclusion

In summary, this study presents preliminary information on the research progress, development trends, research frontiers, and research hotspots of long COVID worldwide through bibliometric and visual analysis, and predicts future research directions, which is of great significance to researchers related to long COVID.

## Funding

Thanks to the support of the Self-Raised Scientific Research Project of the Guangxi Administration of traditional Chinese Medicine (GXZYZ20210005).

## Data availability statement

Data will be made available on request.

## CRediT authorship contribution statement

**Zongqiang Lai:** Data curation, Funding acquisition, Writing – original draft. **Tao Pu:** Data curation, Methodology. **Jun Li:** Formal analysis. **Facheng Bai:** Writing – review & editing. **Lining Wu:** Writing – review & editing. **Yunxia Tang:** Conceptualization, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing

interests:Zongqiang Lai reports financial support was provided by Guangxi Administration of traditional Chinese Medicine.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24053.

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