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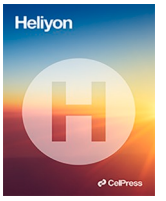

Research article

Mapping the vast landscape of multisystem complications of COVID-19: Bibliometric analysis

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ABSTRACT

Background: With the rapid global spread of COVID-19, it has become evident that the virus can lead to multisystem complications, leading to a significant increase in related publications. Bibliometrics serves as a valuable tool for identifying highly cited literature and research hotspots within specific areas.

Objective: The aim of this study is to identify current research hotspots and future trends in COVID-19 complications.

Methods: The dataset was obtained from the Web of Science Core Collection, covering COVID-19 complications from December 8, 2019, to October 31, 2022. Various aspects, including publication general information, authors, journals, co-cited authors, co-cited references, research hotspots, and future trends, were subjected to analysis. Visual analysis was conducted using VOSviewer, The Online Analysis Platform of Literature Metrology, and Charticulator.

Results: There were 4597 articles in the study. The top three countries with the most published articles are the USA (n = 1350, 29.4 %), China (n = 765, 16.6 %), and Italy (n = 623, 13.6 %). USA and China have the closest collaborative relationship. The institute with the largest number of publications is Huazhong University of Science and Technology, followed by Harvard Medical School. Nevertheless, half of the top 10 institutes belong to the USA. "Rezaei, Nima" published 13 articles and ranked first, followed by "Yaghi, Shadi" with 12 articles and "Frontera, Jennifer" with 12 articles. The journal with the largest number of publications is "Journal of Clinical Medicine". The top 3 co-cited authors are "Zhou, Fei", "Guan, Wei-Jie", "Huang, Chaolin". The top 3 co-cited references addressed COVID-19's clinical features in China and noticed that COVID-19 patients had a wide range of complications. We also list four research hotspots.

Conclusions: This study conducted a bibliometric visual analysis of the literature on COVID-19 complications and summarized the current research hotspots. This study may provide valuable insights into the complications of COVID-19.

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the source of the new acute infectious disease known as Coronavirus disease 2019 (COVID-19). It was initially identified in Wuhan, China, in December 2019, and it quickly spread throughout the world to become a major global health issue [1,2]. Globally, COVID-19 has dramatically harmed the world's health system and people's health. As of October 31, 2022, there were 628,209,690 confirmed cases of COVID-19, including 6,576,928 deaths [3]. COVID-19 patients experience a wide range of symptoms from mild to severe illness, such as fever, dry cough, and shortness of breath. Other common symptoms include new loss of taste or smell, sore throat, and headache [4,5]. Antiviral drugs and vaccines have been developed to protect people, such as Remdesivir, Paxlovid, and Azvudine. These drugs effectively reduce the risk of severe COVID-19 or mortality [6–9]. However, the global COVID-19 pandemic persists, with ongoing challenges posed by SARS-CoV-2 mutations.

Most importantly, SARS-CoV-2 invades the respiratory system and attacks multiple organ systems [10]. The underlying mechanisms have not been fully elucidated. In addition to direct viral attack, dysregulation of the immune response, imbalance of the renin-angiotensin-aldosterone system (RAAS) and endothelial cell damage are involved. The angiotensin-converting enzyme 2 (ACE2) receptor is a binding site for the SARS-CoV-2 spike (S) protein, which allows it to enter host cells. Since ACE2 is highly expressed in the human body, COVID-19 may potentially target every location where ACE2 is expressed, including the neurological system, liver, kidneys, blood vessels, and gastrointestinal tract. Furthermore, ACE2 has a role in the control of RAAS [11,12]. SARS-CoV-2 can cause myocardial injury, arrhythmias, and coagulation abnormalities [13]. Besides, SARS-CoV-2 is neurotropic and hepatotropic, individuals without a history of liver illness may sustain liver damage, and common neurological symptoms are altered mental status, headache, and gustatory and olfactory dysfunctions [14,15]. Therefore, COVID-19 is a multisystem disease. Until now, there has been no specific treatment for the complications of COVID-19. In this context, COVID-19 complications have become a significant problem.

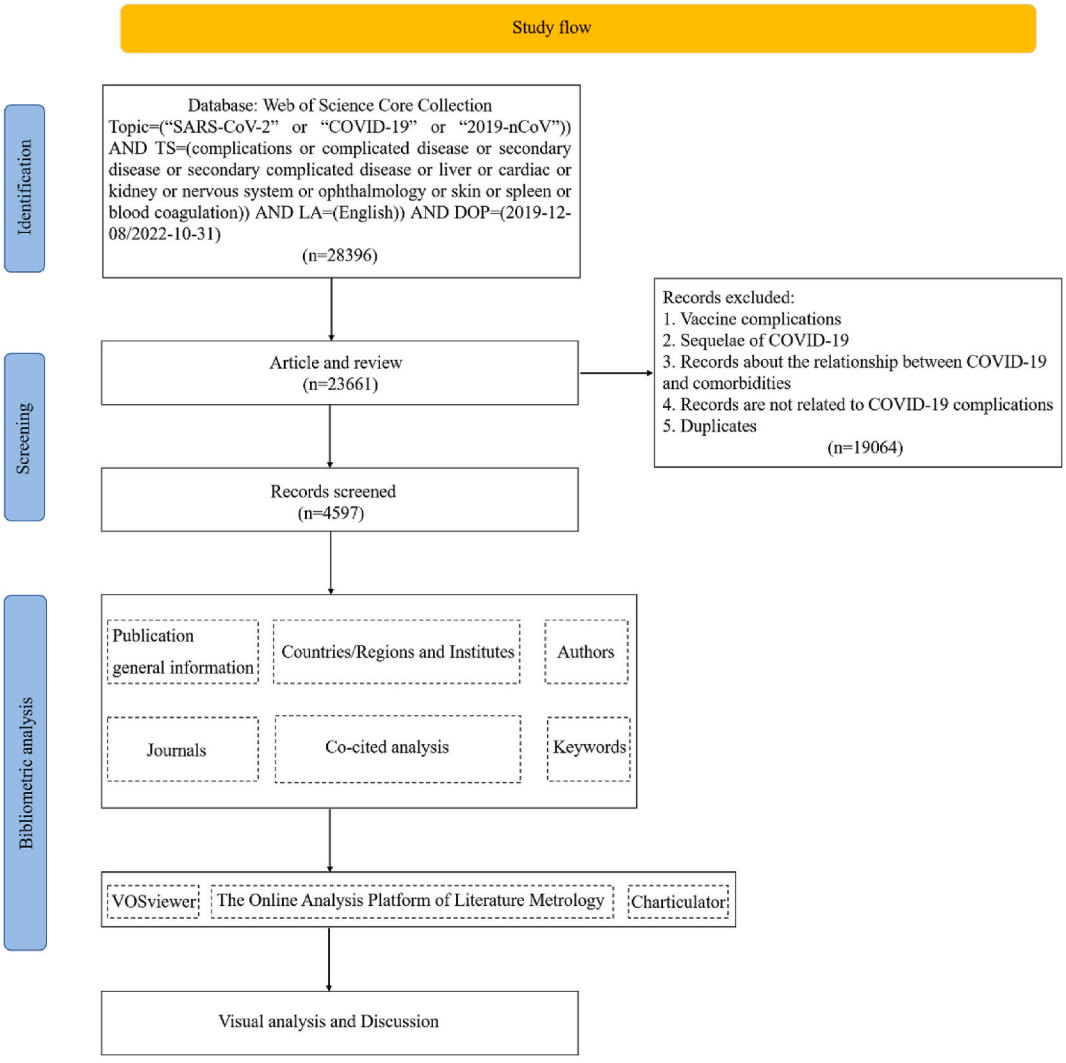

Fig. 1. Study flow.

Bibliometrics is a quantitative research method employed to analyze extensive literature, summarizing various aspects such as the number of publications, authors, and keywords within a specific field [16]. In 2021, Yang et al. conducted a bibliometric study on the complications and sequelae of COVID-19, encompassing 1025 articles published from the inception of the Web of Science (WOS) until December 30, 2020 [17]. Given that three years have elapsed since the onset of the COVID-19 pandemic and with the emergence of mutated strains leading to an increasing number of infections, studies on COVID-19 complications have proliferated, enhancing our understanding of the disease. We performed a thorough bibliometric study of COVID-19 complications in an attempt to present a thorough overview of the condition as well as to outline current research trends and future prospects. This analysis includes a greater amount of literature (4597 articles) and a longer time period (December 8, 2019, to October 31, 2022).

2. Methods

2.1. Data source and search strategy

The dataset was obtained from the WOS Core Collection. WOS is a high-quality literature database accepted by many researchers and is considered the most suitable database for bibliometric analysis [18]. The literature on the complications of COVID-19 was restricted to the period between December 8, 2019, and October 31, 2022. The search terms were "(((TS=("SARS-CoV-2" or "COVID-19" or "2019-nCoV")) AND TS=(complications or complicated disease or secondary disease or secondary complicated disease or liver or cardiac or kidney or nervous system or ophthalmology or skin or spleen or blood coagulation)) AND LA=(English)) AND DOP=(2019-12-08/2022-10-31)".

2.2. Data extraction

Two reviewers (YZ and XYC) independently searched the literature. As we could not complete the literature screening in one day, we downloaded the literature and screened it by two reviewers independently. Two more reviewers (RTY and KL) help to check the results and resolve disagreements [17].

2.3. Data analysis

Publication general information was obtained from WOS, The Online Analysis Platform of Literature Metrology [19] was used to map the number of literature published each year. VOSviewer (version 1.6.18) is a tool for constructing and visualizing bibliometric networks. These networks may include journals, authors, and institutes, keywords [20]. This study used VOSviewer to obtain authors, countries/regions and institutes, co-citation analysis, journals, and keywords information. VOSviewer performed the network visualization map of co-cited authors and keywords. Charticulator [21] was used to examine the cooperative relationship between countries/regions, and OpenRefine (version 3.7-beta2) was used to standardize the name of the institutes. Fig. 1 illustrates the thorough screening procedure.

3. Results

3.1. Publication general information

The search was conducted on November 25, 2022, resulting in an initial yield of 28,396 documents. Following manual screening and removal of duplicates, 4597 documents were included, comprising 2960 (64.4 %) articles and 1637 (35.6 %) review articles. Fig. 2 illustrates the distribution of publications per year. The majority of articles on COVID-19 complications were published in 2021 (n = 2,413, 52.5 %). This surge in publications may be attributed to the escalating number of SARS-CoV-2 infections during that period. However, 2020 also saw a substantial number of publications (n = 1,762, 38.3 %), indicating an early awareness among scientists and

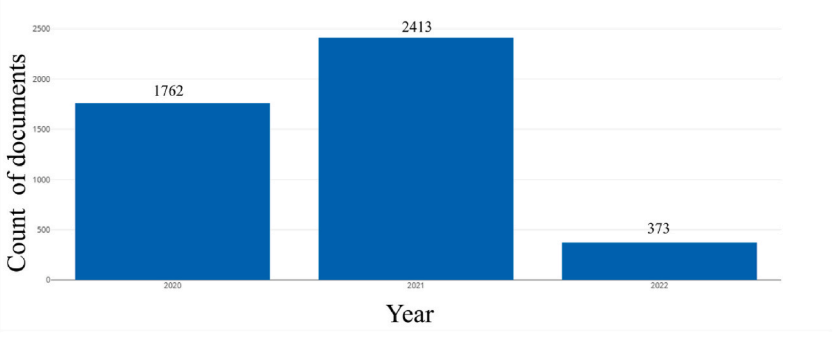

Fig. 2. The annual number of publications on COVID-19 complications (Created on https://bibliometric.com/).

physicians regarding COVID-19 complications.

3.2. Countries/regions and institutes

Articles on COVID-19 complications have been published by 122 countries/regions and 6736 organizations. Table 1 lists the top 10 most active countries/regions, with European countries leading the list, in line with earlier research [17]. The USA (n = 1350, 29.4 %), China (n = 765, 16.6 %), and Italy (n = 623, 13.6 %) emerge as the top three countries with the highest number of published articles. This may be related to the fact that these countries have many COVID-19 patients, it is easy for researchers to observe COVID-19 complications and contribute to this field. Table 2 presents the top 10 most active institutes. To mitigate discrepancies arising from variations in institute names, we employed OpenRefine (version 3.7-beta2) to automatically cluster the institutes' names. Subsequently, we manually cross-referenced the clustering results to identify instances of the same institute and obtained standardized names. Leading the list is Huazhong University of Science and Technology, with 160 articles, followed closely by Harvard Medical School, with 132 articles. Nevertheless, half of the top 10 institutes belong to the USA, demonstrating the country's leadership in this subject, this is consistent with economic conditions because scientific research needs economic support. Meanwhile, VOSviewer and Charticulator were used to examine the collaboration between countries/regions based on the quantity of publications. In Fig. 3, publications from different countries/regions are represented by arcs of different colors. The arc size represents the number of publications, and the link between the arcs represents the intensity of cooperation between countries/regions. As shown in Fig. 3, USA and China have the closest collaborative relationship, USA and Italy also have a close collaborative relationship. As another study has shown, the USA is leading international collaborative efforts, and although China has published many articles, its national cooperation is not active [22]. Cooperation between countries is essential in emerging infectious diseases, and timely data exchange is vital in disease awareness, prevention, and treatment [23]. Therefore, we suggest that researchers from different countries share research data and work together to deal with the complications of COVID-19.

3.3. Authors

A total of 33,888 authors have published articles on COVID-19 complications. Table 3 lists the top 10 most prolific authors. Among these authors, half of them are from the USA. "Rezaei, Nima" published 13 articles and ranked first, followed by "Yaghi, Shadi" with 12 articles and "Frontera, Jennifer" with 12 articles. "Rezaei, Nima" summarized the neurologic manifestations of COVID-19 patients and highlighted the importance of hyperinflammation in the neurological complications of COVID-19 [24,25]. She also discussed the potential association of COVID-19 with anosmia and stroke risk [26,27]. In addition, she is concerned about the autoimmune, cardiovascular, and cutaneous complications of COVID-19 [28–31]. "Yaghi, Shadi" and "Frontera, Jennifer" belong to the same institute. They focused on neurological complications of COVID-19, such as ischemic stroke and intracerebral hemorrhage [32–34]. They studied the clinical characteristics, stroke mechanisms, and outcomes of stroke patients with COVID-19. Their research showed that hypercoagulable states might lead to a high incidence of stroke in COVID-19 and this risk is difficult to detect by imaging [35]. They also found that COVID-19 patients with neurological complications had a higher risk of in-hospital mortality and worse functional outcomes than those without [36,37]. Notably, "Metra, Macro" didn't publish the most articles, but he had the highest citation among the 10 authors. For example, "Metra, Macro", as the corresponding author, published an article entitled "Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19)" in JAMA Cardiology in 2020, which highlighted cardiac involvement as a complication associated with COVID-19 and gained substantial attention [38].

3.4. Co-citation analysis

Co-cited authors indicate that another article cited their article at the same time. Author co-citation analysis serves as a valuable tool in identifying researchers working within similar scientific domains and revealing their interconnections through shared citations, thereby offering insights into the development and structure of knowledge within these fields. Co-cited reference means that two articles are cited by a third article. Articles with a high frequency of co-citation relationships may share similar methods or topics. Given that co-cited authors are identified based on their articles, we will analyze their works collectively below. We focus on the

Table 1
The top 10 countries/regions.

Rank	Countries/Regions	Publications	Citations
1	USA	1350	84377
2	China	765	62785
3	Italy	623	31749
4	England	325	24569
5	Iran	246	5651
6	India	239	7259
7	Germany	235	18626
8	Spain	231	8180
9	France	204	12555
10	Brazil	187	5724

Table 2
The top 10 institutes.

Rank	Institutes	Country	Publications	Citations
1	Huazhong University of Science & Technology	China	160	25569
2	Harvard Medical School	USA	132	15250
3	Wuhan University	China	97	22567
4	University of Milan	Italy	81	4842
5	Tehran University of Medical Sciences	Iran	68	1739
6	Icahn School of Medicine at Mount Sinai	USA	58	6650
7	Mayo Clinic	USA	58	5258
8	Columbia University	USA	56	7615
9	Massachusetts General Hospital	USA	54	4828
10	University of Paris	France	51	5822

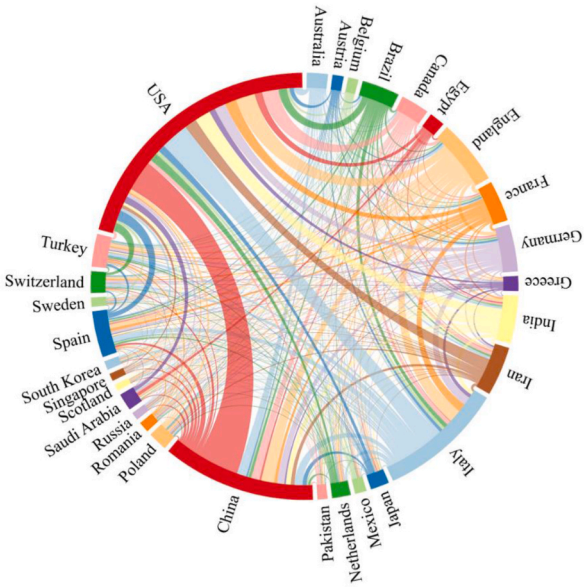

Fig. 3. The cooperation of countries/regions (Created on https://charticulator.com/).

Table 3
The top 10 most prolific authors.

Rank	Author	Article counts	Citations	Country	H-index
1	Rezaei, Nima	13	255	Iran	48
2	Yaghi, Shadi	12	1015	USA	39
3	Frontera, Jennifer	12	788	USA	40
4	Metra, Macro	9	1435	Italy	36
5	Jhaveri, Kenar D.	9	1165	USA	31
6	Long, Brit	9	728	USA	27
7	Andina-Martinez, David	9	548	Spain	8
8	Torrelo, Antonio	9	548	Spain	33
9	Zand, Ramin	9	357	USA	10
10	Pelosi, Paolo	9	236	Italy	34

relationships among the top ten highly influential and highly co-cited authors. To effectively visualize co-citation patterns among these authors with substantial impact, we selected 15 authors to draw co-citation maps. Fig. 4 shows the top 15 co-cited authors. They have all been co-cited more than 500 times. In Fig. 4, a node represents the author, and node size represents the number of citations. The larger the node, the higher the number of citations. The shorter the distance between nodes, the closer the connection between authors. Colors indicate clusters. The lines between nodes represent co-citation relationships, with thicker lines indicating stronger ones. There are two clusters:

Cluster 1 (red): “chen, ns”, “guan, w”, “huang, cl”, “shi, sb”, “wang, dw”, “world health, organization”, “zhou, f”, “zhu, n”.

Cluster 2 (green): “hamming, i”, “helms, j” “hoffmann, m”, “klok, fa”, “mao, l”, “tang, n”, “varga, z”.

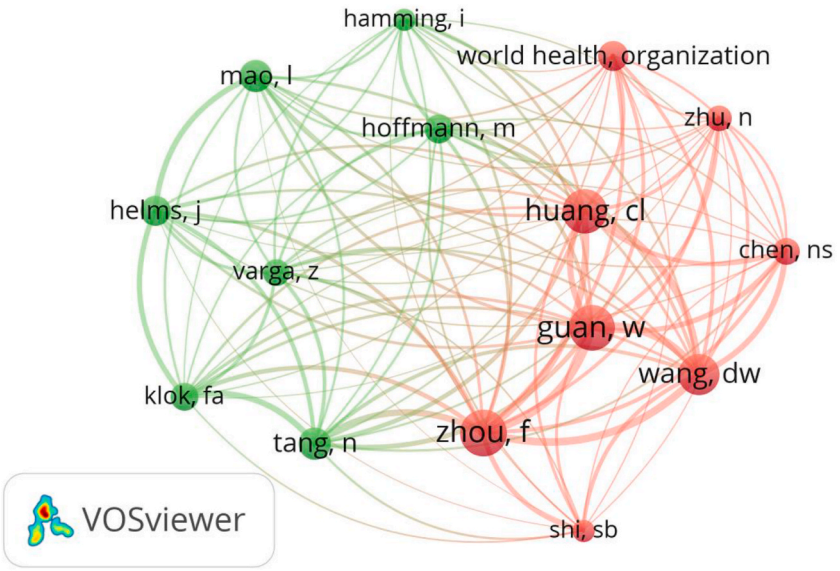

Fig. 4. Top 15 co-cited authors.

Table 4 lists the top 10 co-cited articles. They were all co-cited over 600 times and the top 3 references were co-cited over 1000 times. Surprisingly, the top 10 co-cited articles were all published in 2020, indicating that physicians and scientists noticed COVID-19 complications early in the pandemic.

In the red cluster of Fig. 4, "Zhou, F" (Zhou, Fei) from China-Japan Friendship Hospital exhibits the strongest centrality, followed by "Guan, W" (Guan, Wei-Jie) from the First Affiliated Hospital of Guangzhou Medical University and "Huang, CL" (Huang, Chaolin) from Jin Yin-tan Hospital. Their research focused on the clinical characteristics of COVID-19 patients in China, identifying a wide array of complications such as cardiac, renal, and coagulation disorders [39–41]. "Zhu, N" (Zhu, Na) and "Chen, NS" (Chen, Nanshan) also conducted similar studies [42,43]. In the green cluster, "Tang, N" (Tang, Ning) and "Klok, FA" (Klok, F. A.) emphasized the thrombotic complications of COVID-19 [44,45]. "Mao, L" (Mao, Ling) provided a summary of neurological manifestations observed in hospitalized COVID-19 patients [46]. Additionally, "Hoffmann, M" (Hoffmann, Markus) revealed that SARS-CoV-2 enters cells via ACE2, which is widely distributed in the body and implicated in various complications [47], while "Varga, Z" (Varga, Zsuzsanna) further discovered that ACE2 expression extends to endothelial cells, potentially contributing to cardiovascular and digestive system complications through diffuse endothelial inflammation [48].

Obviously, these articles have been published in excellent journals, providing a solid basis for subsequent research.

Table 4
Top 10 co-cited references.

Rank	Title	First Author	Journal	Total counts of co-citations	Publication time
1	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	Zhou, Fei	Lancet	1209	2020
2	Clinical Characteristics of Coronavirus Disease 2019 in China	Guan, Wei-Jie	The New England journal of medicine	1170	2020
3	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	Huang, Chaolin	Lancet	1098	2020
4	Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia	Tang, Ning	Journal of thrombosis and haemostasis: JTH	675	2020
5	Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China	Mao, Ling	JAMA Neurology	658	2020
6	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	Chen, Nanshan	Lancet	643	2020
7	A Novel Coronavirus from Patients with Pneumonia in China, 2019	Zhu, Na	The New England journal of medicine	613	2020
8	SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor	Hoffmann, Markus	Cell	612	2020
9	Incidence of thrombotic complications in critically ill ICU patients with COVID-19	Klok, F. A.	Thrombosis Research	611	2020
10	Endothelial cell infection and endotheliitis in COVID-19	Varga, Zsuzsanna	Lancet	602	2020

3.5. Journals

Table 5 lists the 10 journals with the largest number of articles, "Journal of Clinical Medicine" ranked first with 91 articles, followed by "Frontiers in Medicine" with 78 articles and "Plos One" with 60 articles. Among the top 10 most active journals, "Journal of Medical Virology" has the most citations (n = 3656), which may indicate that "Journal of Medical Virology" has published many articles on COVID-19 complications and received much attention. For example, the article "The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients" suggests that SARS-CoV-2 possesses neuroinvasive capabilities, potentially influencing the management of SARS-CoV-2 induced respiratory failure [49]. Meanwhile, there are four journals owned by frontiers: Frontiers in Medicine, Frontiers in Neurology, Frontiers in Cardiovascular Medicine, Frontiers in Immunology, indicating its advantages in this field.

3.6. Keywords

High-frequency keywords can reveal the hot topics in the research field, which helps analyze the research hotspots and frontiers in a specific field. A total of 8014 keywords were screened by thematic cluster analysis of the literature, in order to include more meaningful keywords and draw clear graphics, 60 keywords with frequency ≥70 were selected for analysis (Fig. 5, Table 6). Statistics of keywords occurrences frequency in Table 6 indicate an unbalanced distribution with a wide span of 70 to 3136. In Fig. 5A, node size represents keywords occurrence frequency. Links between nodes and the strength of the link illustrate the number of times that two keywords occur together in one study. Different colors represent different clusters, namely different research topics. To systematically understand the concrete focus topics, keywords cluster analysis is shown in Fig. 5B. The density of keywords is shown in Fig. 5C. Based on different keywords clusters, four themes are identified: Cluster 1 "SARS-CoV-2 infection and pathogenesis", Cluster 2 "Epidemiology and clinical characteristics", Cluster 3 "Coagulation abnormalities and thrombosis", Cluster 4 "Specific groups and myocardial injury". Fig. 5D is the overlay visualization of keywords' average publication year, with different colors representing different average publication time, ranging from far to near in time and from blue to green to yellow.

4. Discussion

4.1. General information

In recent years, a substantial body of literature consisting of 4597 articles has attested to the increasing focus on COVID-19 complications. Comparing with previous study [17], The United States, China, and Italy continue to dominate the publication landscape, with China overtaking Italy to occupy the second position. These three nations remain the epicenters international collaboration in this field. Among institutions, Huazhong University of Science & Technology maintains its status as the most productive, whereas Harvard Medical School has advanced from sixth to second place. The emergence of a new cohort of top ten authors reflects the intensified engagement of scholars in COVID-19 complications research. Co-citation analysis identifies "Huang, Chaolin", "Zhou, Fei", "Guan, Wei-Jie", and "Chen, Nanshan" as prominent co-cited authors in this domain. Notably, "Journal of Clinical Medicine" has supplanted "Journal of Medical Virology" as the most frequently publishing journal. Concurrently, there is a discernible shift in research priorities, with a gradual shift from a predominant emphasis on epidemic outbreaks towards investigations of COVID-19 complication prevalence, outcomes, and the association with venous thromboembolism.

4.2. Research hotspots

Keywords provide a summarized description of an article's significant contents and points. Different keyword clusters reveal intrinsic connections and developmental trends among articles within the field. As mentioned, four clusters were identified in COVID-19 complications, capturing four research topics. The following section will briefly discuss the research hotspots and future trends in COVID-19 complications.

Table 5
Top 10 most active journals.

Rank	Source	Document counts	Total counts of citations
1	Journal of Clinical Medicine	91	1624
2	Frontiers in Medicine	78	875
3	Plos One	60	1233
4	Frontiers in Neurology	58	1113
5	Journal of Medical Virology	53	3656
6	Frontiers in Cardiovascular Medicine	42	404
7	Medicine	39	261
8	Frontiers in Immunology	37	1209
9	World Journal of Gastroenterology	34	455
10	American Journal of Emergency Medicine	33	1238

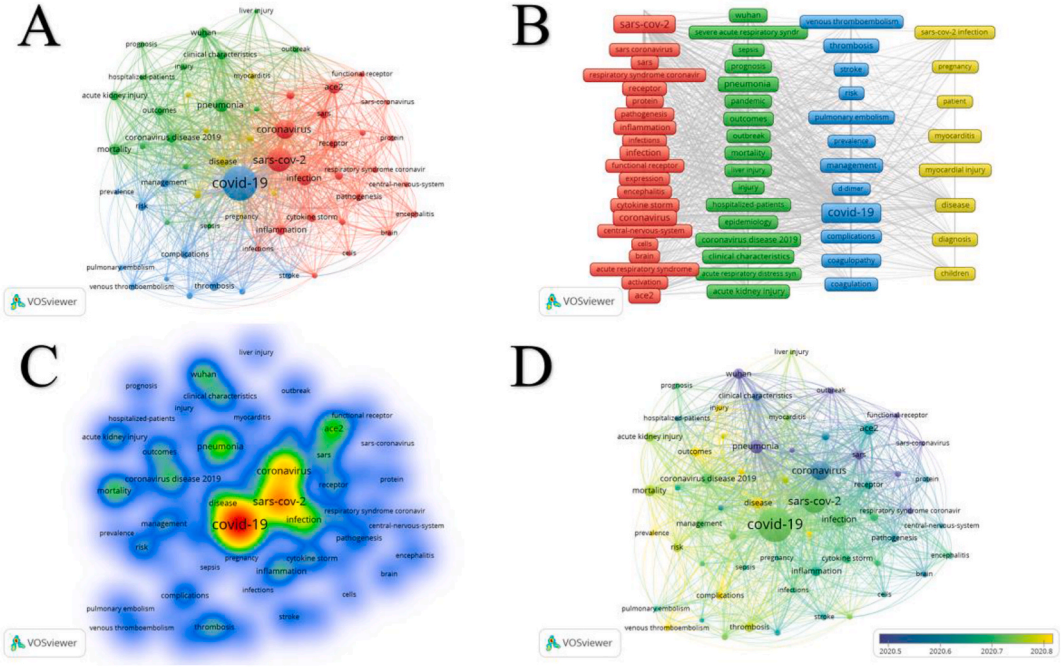

Fig. 5. Keywords of articles about COVID-19 complications. (A) Keywords distribution. (B) Keywords cluster separation. (C) The density of keywords. (D) Timelines of keywords.

4.3. Cluster 1: SARS-CoV-2 infection and pathogenesis

This cluster focuses on the infection and pathogenic mechanism of SARS-CoV-2. On the one hand, both SARS-CoV and SARS-CoV-2 are coronaviruses that can cause severe respiratory diseases in humans, and their associated illnesses, SARS and COVID-19, share similar symptoms like fever, cough, and dyspnea [50]. On the other hand, SARS-CoV and SARS-CoV-2 also share many similarities in genetic makeup and transmission patterns [47,51,52]. Research in the field can provide insights into the pathogenesis, treatment, and management of COVID-19 and its complications based on previous studies on SARS and SARS-CoV. The mechanism by which the virus enters host cells is an aspect of the cluster. Both SARS-CoV and SARS-CoV-2 rely on the same receptor ACE2 to enter host cells [47]. Transmembrane protease serine 2 (TMPRSS2) and host protease L/B mediate the activation of the viral S protein [47,52]. The interaction between viral S protein and membrane-bound enzyme ACE2 promotes the entry of SARS-CoV and SARS-CoV-2 into host cells and subsequently down-regulates surface ACE2 expression [47,53]. The wide distribution and expression of ACE2 in multiple organs and tissues allow for multisystem complications of COVID-19 [12]. Certain cell types in the small intestine, pancreas, kidneys, adipose tissue, lungs, cardiovascular system, central nervous system, testes, and placenta have been shown to express ACE2 [53,54]. In addition, as a regulator of the RAAS, ACE2 maintains the homeostasis of RAAS by inactivating Angiotensin II [55,56]. The interaction between ACE2 and SARS-CoV-2 causes the down-regulation of ACE2, promoting systemic imbalance of RAAS and further exacerbating the multisystem complication caused by SARS-CoV-2 infection [53,57].

The neurological complications caused by SARS-CoV-2 infection and its mechanisms are an extended focus in this cluster. SARS-CoV-2 can invade the nervous system through a variety of routes. ACE2 receptor is widely expressed in neurons, astrocytes, pericytes, and smooth muscle cells of brain blood vessels, providing a possible gateway for SARS-CoV-2 to invade the central nervous system [58]. Direct evidence suggests that SARS-CoV-2 mainly infects choroid plexus epithelium (high ACE2 expression), leading to brain barrier damage, and SARS-CoV-2 can be detected in cerebrospinal fluid [59,60]. Access to the central nervous system from peripheral nerves, such as olfactory sensory neurons, the pulmonary network, or the enteric nervous system, is possible. Exacerbating inflammation and pneumonia-induced hypoxia in the nervous system caused by SARS-CoV-2 are indirect factors that have gained substantial attention [61].

Hospitalized COVID-19 patients frequently experience neurological complications. A retrospective clinical study of 509 COVID-19 patients found that 419 (82.3 %) patients had neurological symptoms at any time. Frequent neurologic manifestations were myalgias (44.8 %), headaches (37.7 %), encephalopathy (31.8 %), dizziness (29.7 %), dysgeusia (15.9 %), and anosmia (11.4 %). Strokes, movement disorders, motor and sensory deficits, ataxia, and seizures were uncommon [62]. Patients who have recovered from COVID-19 may continue to experience olfactory and gustatory impairment, which has been documented as an early neurological manifestation in COVID-19 patients [63,64]. Another study of 236,379 COVID-19 survivors found that more than one-third had a neurological or psychiatric disease within six months of COVID-19 diagnosis, implying a higher risk of neurological or psychiatric diagnoses in COVID-19 survivors [65]. Unsurprisingly, some neurological symptoms, such as encephalopathy, are associated with

Table 6
Top 60 most used keywords.

keyword	Rank	Occurrences	Total link strength
covid-19	1	3136	8623
sars-cov-2	2	1535	5242
coronavirus	3	976	3697
infection	4	557	2337
pneumonia	5	480	2154
ace2	6	414	1925
disease	7	334	1294
mortality	8	322	1118
wuhan	9	296	1363
coronavirus disease 2019	10	282	998
inflammation	11	256	1065
clinical characteristics	12	247	1122
sars	13	241	1109
outcomes	14	241	989
thrombosis	15	235	897
acute kidney injury	16	231	842
receptor	17	207	1016
cytokine storm	18	205	911
management	19	199	838
risk	20	193	791
complications	21	186	666
acute respiratory syndrome	22	171	777
expression	23	171	771
pathogenesis	24	165	826
children	25	152	468
diagnosis	26	142	532
stroke	27	138	521
myocarditis	28	136	482
injury	29	128	519
venous thromboembolism	30	123	456
outbreak	31	121	652
coagulopathy	32	116	506
encephalitis	33	114	498
epidemiology	34	110	442
brain	35	109	570
respiratory syndrome coronavirus	36	107	538
protein	37	103	513
prognosis	38	103	347
virus	39	101	524
coagulation	40	99	419
sars coronavirus	41	98	477
hospitalized-patients	42	96	495
functional receptor	43	96	483
sars-cov-2 infection	44	95	357
pulmonary embolism	45	94	337
activation	46	91	379
myocardial injury	47	89	341
pandemic	48	87	367
severe acute respiratory syndrome coronavirus 2	49	86	307
central-nervous-system	50	84	342
patient	51	83	314
infections	52	83	336
sepsis	53	82	304
pregnancy	54	78	260
cells	55	77	344
sars-coronavirus	56	74	365
liver injury	57	73	275
acute respiratory distress syndrome	58	72	226
d-dimer	59	70	285
prevalence	60	70	282

worse clinical outcomes [62].

The cluster keywords also focus on cytokine storms and the activation of related pathways. In SARS-CoV-2 infection, the virus infects epithelial cells. It activates innate immune cells to produce proinflammatory cytokines or chemokines, which can continue to attract and activate more immune cells, producing sustained inflammatory cytokines, amplifying the cascade effect of inflammation, and causing immune dysregulation [66,67]. COVID-19 patients, especially severe patients, show an increase in neutrophils and a decrease in lymphocytes in their peripheral blood, along with elevated levels of proinflammatory cytokines [68]. They also exhibit a

delayed interferon (IFN) response, with insufficient IFN-I expression in the early stages of infection and increased levels of IFN-α in the peripheral blood in the later stages of severe COVID-19 [69,70]. This delayed but heightened IFN-I response exacerbates the excessive inflammatory state in severe COVID-19 [71,72]. Delayed immune response and excessive inflammation in SARS-CoV-2 infection can induce the accumulation of monocytes and macrophages and the release of various proinflammatory cytokines and chemokines, further triggering a cytokine storm, leading to severe complications and adverse outcomes, including acute respiratory distress syndrome (ARDS)), multiple organ dysfunction syndrome, and even death [67,73,74]. When SARS-CoV-2 enters host cells, it is recognized by pattern recognition receptors, containing toll-like receptors (TLR)3, TLR7, TLR8, retinoic acid-inducible gene-1, differentiation-associated gene 5 and NOD-like receptors. It activates downstream transcription factors such as IFN regulatory factor 3/7 and nuclear factor-κB (NF-κB), leading host cells to produce IFN-I and proinflammatory cytokines. However, the virus can cancel the IFN-I response through different mechanisms, leading to excessive secretion of proinflammatory cytokines such as interleukin (IL)-6, IL-2, tumor necrosis factor (TNF)-α, and IFN-γ [66,75]. Furthermore, these cytokines activate Janus kinase-signal transducer and activator of transcription (JAK-STAT) or NF-κB signaling by binding to receptors expressed on immune cells, creating positive proinflammatory feedback, and inducing cytokine storms [66]. This process involves multiple signaling pathways, such as angiotensin II/AT1R, ACE2, innate immune signaling pathways, and various receptors [75].

4.4. Cluster 2: epidemiology and clinical characteristics

The keywords in this cluster mainly focus on the epidemiology of COVID-19 and its diverse clinical manifestations. COVID-19 was discovered in Wuhan, China, in November 2019 and has since become a global pandemic. It involves multiple organ systems, and patients may present with a wide range of clinical characteristics, ranging from asymptomatic to severe or even fatal [76]. Typical symptoms include fever, cough, and dyspnea, other symptoms that are frequently experienced include nausea, vomiting, diarrhea, anosmia, ageusia, sore throat, and headache [39,46]. In addition, the infection may also lead to various complications that cause severe illness and death, including pneumonia, ARDS, liver injury, myocardial injury, thrombosis, acute kidney injury (AKI), neurological disorders, and sepsis, among others [40,41].

Among hospitalized COVID-19 patients, 15%–30 % may develop ARDS due to the SARS-CoV-2 infection, and COVID-19-related deaths are often associated with ARDS, which may be caused by cytokine storms [77,78]. In addition, ARDS is more common in elderly patients with COVID-19 [39]. Some COVID-19 patients with ARDS, who received mechanical ventilation treatment, seemed to acquire pneumothorax/pneumomediastinum as a common complication regardless of the mechanical ventilation setting [44]. Furthermore, spontaneous pneumothorax was reported as a rare pulmonary complication of COVID-19 patients without intubation [79]. Additionally, extensive pulmonary vascular thrombosis may lead to pulmonary embolism [80], which has been observed in severe COVID-19 patients and is a direct cause of death in several COVID-19 patients [81,82]. Pulmonary fibrosis can be a long-term pulmonary result of severe COVID-19 patients, and symptoms can range from asymptomatic to respiratory failure and even ARDS [83,84]. Dyspnea was also common in patients recovering from COVID-19 [85]. The abnormal test results in discharged COVID-19 patients suggest the presence of permanent lung dysfunction [86,87].

Liver injury in COVID-19 can manifest as increased alanine aminotransferase, aspartate aminotransferase, total blood bilirubin, and decreased albumin [88]. The possible causes of liver injury in COVID-19 include direct infection with SARS-CoV-2, indirect involvement of systemic inflammation, and iatrogenic causes such as changes in hypoxia, drugs, and ventilation [14].

ACE2 is also highly expressed in the digestive system, making the digestive system a target for SARS-CoV-2 [89], and autopsy reports support intestinal injury in COVID-19 patients, such as microthrombus in the gastrointestinal tract, hepatic cell degeneration and focal necrosis [90,91]. In addition, stool samples from COVID-19 patients were positive for SARS-CoV-2 RNA, which persisted after respiratory samples were negative [92]. Clinically, gastrointestinal symptoms in COVID-19 ranged from 3 to 79 percent [93]. The digestive manifestations of COVID-19 patients include abdominal pain, diarrhea, anorexia, nausea and vomiting, and elevated liver enzymes [94,95]. Gastrointestinal perforation and upper gastrointestinal bleeding have also been reported [96,97]. Most of these symptoms can be managed without endoscopy because they are not life-threatening [98]. In addition, acute pancreatitis appears to be associated with COVID-19 [99].

Regardless of baseline renal function, AKI is the most prevalent extrapulmonary manifestation of severe COVID-19. Patients often present with hematuria, proteinuria, elevated serum creatinine, and elevated blood urea nitrogen. Although proteinuria, hematuria, and AKI usually resolve within three weeks of symptom onset in some patients, COVID-19 patients with kidney disease have a significantly higher risk for in-hospital death [100–102]. According to an early meta-analysis with 20 cohorts covering 13137 in-patients diagnosed with COVID-19, the frequency of AKI was 17 %, while approximately 5 % of all patients required dialysis [103]. Clinical data [104] showed that 20.6 % of COVID-19 patients in the ICU with AKI were receiving renal replacement therapy. Additionally, electrolyte disturbances are also a common renal complication. In particular, hyperkalemia has been identified as an independent factor for RNA-positive recurrence of SARS-CoV-2 [105,106]. The pathogenesis of renal dysfunction is multifactorial. ACE2 is expressed in the renal proximal tubule [107]. The autopsy reports showed that SARS-CoV-2 RNA accumulated in the renal tubular epithelium [108,109]. This suggests that the virus can infect the kidneys directly, although this mechanism remains controversial. Currently, the main mechanisms of AKI in COVID-19 patients are hemodynamic abnormalities, hypoxia, and cytokine storm [110].

4.5. Cluster 3: coagulation abnormalities and thrombosis

Keywords in this cluster mainly concern COVID-19-related coagulation abnormalities and thrombosis. The incidence of thrombotic complications in ICU severe COVID-19 patients is as high as 31 %. And a high level of D-dimer on admission is a potential risk factor for

poor prognosis [39]. The immune response dysregulation induced by SARS-CoV-2 infection is characterized by widespread endothelial cell damage, complement activation, thrombosis formation, and intravascular coagulation, which is an important mechanism for the progression of COVID-19 [111]. SARS-CoV-2 can activate complement through the lectin pathway, further promoting endothelial cell damage and thrombosis formation within the blood vessels [112]. The complement cascade reaction mediates tissue inflammation and thrombosis, ultimately leading to severe consequences of COVID-19 [112,113]. Autopsy results of COVID-19 patients show complement deposition on the vascular endothelium of multiple organs [114]. COVID-19 patients are more susceptible to systemic thrombotic complications, and the origin of COVID-19 thrombosis is endothelial injury, leading to excessive inflammation, platelet activation, and stasis [115,116]. There is an intrinsic link between virus-mediated endothelial cell damage and platelet activation-mediated coagulation abnormalities in COVID-19 [117,118]. Platelets, endothelial cells, and white blood cells interact to form a complex cross-talk mechanism, and excessive platelet activation exacerbates proinflammatory and procoagulant effects, thereby accelerating thrombosis [117,119].

Coagulation abnormalities are common in severe COVID-19 patients, characterized by high D-dimer levels, fibrin degradation products, platelet activation marker P-selectin, and thrombocytopenia, indicating poor prognosis [45,120,121]. Platelets express toll-like receptors, participate in inflammation, interact with pathogen-associated molecular patterns, activate neutrophils, and form neutrophil extracellular traps [122]. The levels of serum markers for neutrophil extracellular traps, myeloperoxidase-DNA, and citrullinated histone H3, are elevated in COVID-19 patients [123]. The neutrophil-to-lymphocyte ratio can be a prognostic factor for severe COVID-19 [68]. Widespread neutrophil infiltration in the liver, myocardial cells, and pulmonary capillaries is suggested by autopsy pathology, and this is thought to be a key contributor of COVID-19 immunopathology, including cytokine storm [124,125]. Neutrophil activation marker is proven associated with D-dimer, while neutrophil activation and neutrophil extracellular traps release to participate in COVID-19-related thrombosis, which further leads to multiorgan damage [126]. Endothelial injury induced by SARS-CoV-2 infection, complement activation, and platelet activation may trigger pulmonary and renal microvascular blockage occluded by neutrophil extracellular traps [127,128].

Coagulation abnormalities and thrombosis are not only significant complications of SARS-CoV-2 infection, but also a crucial part of the pathogenesis of many other complications associated with COVID-19. Critically ill COVID-19 patients have widespread endotheliitis and microvascular damage, and they may develop systemic thrombotic complications, including pulmonary embolism, deep vein thrombosis, ischemic stroke, and acute coronary syndrome [48,116,129]. Endothelial injury, thrombosis, and exudative diffuse alveolar damage may contribute to ARDS. SARS-CoV-2 induces widespread endothelial damage leading to endothelial inflammation and widespread thrombosis with microangiopathy [80,130]. Autopsies of COVID-19 patients show that exudative diffuse alveolar damage was one of the major pulmonary findings [131,132]. COVID-19 patients have a higher incidence of stroke, and cryptogenic strokes are more common, with a higher proportion of large vessel occlusions [35,133]. There have been reports of hemorrhagic strokes occurring in COVID-19 patients after receiving anticoagulation therapy [134]. Coagulopathy with cerebral hypoxic-ischemic injury and blood-brain barrier abnormalities with endothelial injury are potential pathogenesis for COVID-19-related neurological diseases during the acute phase [58]. Research has found that the plasma of patients with Post-Acute Sequelae of COVID-19 (PASC) contains micro-clots with fibrinolytic resistance, which may help explain the persistent symptoms in PASC patients [135].

4.6. Cluster 4: specific groups and myocardial injury

The keywords in this cluster mainly revolve around two categories: special populations and cardiac damage, such as “pregnancy, children” and “myocarditis, myocardial injury”. Myocardial damage was observed in some COVID-19 patients, with a noticeable elevation of cardiac biomarkers, especially cardiac troponin [136,137]. The major clinical manifestations of cardiac injury caused by SARS-CoV-2 include myocarditis, heart failure, arrhythmias, Takotsubo cardiomyopathy, and long-term adverse remodeling of heart tissue [138,139]. Direct viral damage, cytokine storm, hypoxemia, and endothelial cell injury may be involved in cardiac injury [138,140]. Currently, there is no specific diagnosis method and incidence of myocarditis related to SARS-CoV-2 infection, but it seems more common in men than women [141]. Although troponin elevation is associated with adverse outcomes, it does not support the diagnosis of myocarditis without clinical or radiological evidence [142]. In addition, there is also a risk of myocarditis from vaccination, but it is generally lower than from SARS-CoV-2 infection, so the vaccine is still recommended [143]. Arrhythmias were described as a general cardiovascular complication in COVID-19 patients with an incidence of 19.2 %, which can be divided into tachycardia and bradycardia. Atrial fibrillation is the most common type of arrhythmia and carries a higher mortality risk [144]. With a 20.2 % frequency, heart failure is a frequent consequence in severe COVID-19 patients and is linked to a greater short-term mortality risk [137,145]. Moreover, the risk and one-year burden of cardiovascular diseases in acute COVID-19 survivors have also been reported, independent of cardiovascular risk factors [146].

Some reports suggest that pregnant women have a higher risk of severe illness and death, possibly related to reduced lung capacity, immunological changes, and increased risk of blood clots [147–149]. On the other hand, evidence suggests that SARS-CoV-2 infection during pregnancy is associated with adverse pregnancy outcomes [150].

Children with COVID-19 mostly have mild symptoms, a low probability of developing severe complications, and a good prognosis [151]. However, children with underlying conditions such as obesity and asthma have an increased risk of developing severe COVID-19 [152]. In addition, multisystem inflammatory syndrome in children (MIS-C) is a rare but severe hyperinflammation complication of COVID-19 in children and adolescents [153,154]. MIS-C usually occurs 2–6 weeks after SARS-CoV-2 infection [155]. MIS-C presents a variety of clinical manifestations, including fever, gastrointestinal, cardiovascular, skin, respiratory, and neurocognitive symptoms [156,157]. As some clinical features of Kawasaki disease overlap with MIS-C, it is necessary to distinguish them [158]. There seem to be age and race differences in MIS-C patient groups, Blacks and Hispanics are more likely to have MIS-C [154,

159].

Gender plays a role in COVID-19 outcomes. Men may be more likely to develop severe COVID-19 and have a higher mortality rate [160,161]. Further, age and comorbidities are risk factors for prognosis, while male patients are more vulnerable [162]. Presumably, sex hormones and sex chromosomes cause gender differences by affecting ACE2 and TMPRSS2 expression [163,164]. Endocrine factors, particularly adrenal stress response, may also participate in gender dimorphism in COVID-19 [165]. In addition, other sex-based differences should be concerned, such as lifestyle, mental stress, and socioeconomic status [166].

Interestingly, there appear to be gender differences in the impact of COVID-19 on the reproductive system: male patients with COVID-19 showed a short-term decline in fertility. At the same time, there was no strong association between female COVID-19 infection and fertility [167]. ACE2 is highly expressed in the testis, and high ACE2 levels hinder spermatogenesis, meaning that SARS-CoV-2 may affect male fertility [168]. Male COVID-19 patients showed decreased total testosterone levels and increased luteinizing hormone and prolactin levels [169]. Meanwhile, sperm quality is reduced after COVID-19 infection [170]. However, ACE2 is widely expressed in the female reproductive system, providing the probability of reproductive dysfunction [171,172]. For example, menstrual alterations were described as an effect of COVID-19 on the female reproductive system [173]. Notably, there were fewer clinical reports about COVID-19's reproductive effects in women than in men. Such gender differences may be related to several considerations: sex difference in ACE2 expression, the protective role of female sex hormones, and the detrimental role of androgens, although all these suppositions lacked solid evidence [174]. However, the female gender appears to be a risk factor for post-acute COVID-19 syndrome [175].

5. Future trends

According to Fig. 5D, "prevalence, outcomes, venous thromboembolism" are the latest hot topics. Although the epidemiology of complications of various systems is described above, there is no definite report on them. Venous thrombosis plays an important role in the COVID-19 complications and may participate in the subsequent development of the sequelae of the COVID-19, so it is also a research hotspot.

6. Limitations

Although our article included a large amount of literature, our data came from WOS, and we only included English literature. It must be admitted that WOS, despite its reliability, can not include all literature. There is also a risk that our search string, though carefully described, may be unable to include all the articles on the complications of COVID-19. Additionally, our article did not include preprint articles. Although preprints may contain cutting-edge information, the quality of articles not peer-reviewed may not be guaranteed. In addition, new literature is constantly being published, and original articles are constantly being cited during our analysis, which may also impact our study. However, our research literature has a long period, and we used visual analysis. It will provide a reliable summary of COVID-19 complications and a reference for future research.

7. Conclusion

With the invention of antiviral drugs and vaccines, the treatment of the COVID-19 pandemic is gradually under control. Scientists have paid much attention to the systemic complications of COVID-19 because they affect the length of hospital stay and mortality. This study depicted a comprehensive landscape of research on complications of COVID-19 complications. We evaluated the characteristics of current publications, identified the most influential countries/regions, institutions, journals, and authors, and described the research hotspots and trends in this field. The prevalence of COVID-19 complications, the pathological mechanisms of venous thrombosis in the disease, and the outcomes of COVID-19 complications may be recent research hotspots.

Ethical approval

The data from a subscription-based database that is built upon published data was used. It is important to note that our research did not involve any experiments involving human or animal participants. Approval from the ethics committee is unnecessary.

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Data availability

The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Yi Zhu: Writing – original draft, Methodology, Data curation. **Xiyu Cao:** Writing – original draft, Data curation. **Rongtao Ying:** Writing – original draft, Visualization, Data curation. **Ke Liu:** Writing – original draft, Visualization, Methodology, Data curation. **Yilu Chai:** Writing – original draft, Data curation. **Maocai Luo:** Software, Data curation. **Qingsong Huang:** Writing – review & editing, Conceptualization. **Peiyang Gao:** Writing – review & editing, Methodology, Conceptualization. **Chuantao Zhang:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

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.

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CTZ and QSH provided the idea of this manuscript, YZ and MCL reviewed the literature, YZ and XYC extracted the literature, RTY and KL completed the bibliometrics part, YLC wrote the review section on complications of COVID-19, YZ and XYC wrote the first draft of this manuscript. CTZ, QSH and PYG contributed to the manuscript revision. All authors read and approved the submitted version.

Abbreviations

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
RAAS	renin–angiotensin-aldosterone system
ACE2	angiotensin-converting enzyme 2
WOS	Web of Science
ARDS	acute respiratory distress syndrome
AKI	acute kidney injury
MIS-C	multisystem inflammatory syndrome in children
TMPRSS2	Transmembrane protease serine 2
IFN	interferon
TLR	toll-like receptors
NF-κB	nuclear factor-κB
IL	interleukin
TNF	tumor necrosis factor
JAK	Janus kinase
STAT	signal transducer and activator of transcription

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