

Emerging Trends and Research on Hydroxychloroquine Treatment in Diseases From 1991 to 2020

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Research

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Abstract

Background Recently, hydroxychloroquine (HCQ) has become a controversial point for whether it functioned in the treatment of coronavirus disease 2019 (COVID-19). The aim of this paper is mainly to explore the international frontiers and trends of HCQ clinical treatment in recent 30 years by bibliometric analysis. Besides, the research prospects and hotspots of HCQ therapy in COVID-19 have further been investigated quantitatively and qualitatively.

Methods Publications related to HCQ treatment research from 1991 to 2020 and HCQ studies on COVID-19 from the end of 2019 till now were both obtained from Web of Science Core Collection (WOSCC). Bibliometric analyses were primarily performed via Citespace 5.7.R1 to identify the trends of cooperation between countries and institutions, the research hotspots and frontiers.

Results A total of 2642 articles and reviews on HCQ treatment in diseases were included, indicating an increase in number of publications since 2013. The United States was the largest scientific output country, followed by France and China. Trending keywords analysis indicated the hotspot research of HCQ treatment referred to “rheumatoid arthritis,” “chloroquine”, “systemic lupus erythematosus” and “COVID-19”. Moreover, 568 publications on the study of HCQ in COVID-19 therapy were also gathered from WOSCC, which showed the USA ranked first again in the world for its most publications. Further, Aix Marseille University, Univ Tehran Med Sci, Univ Paris, Harvard Med Sch and Huazhong Univ Sci & Technol were the five leading institutions in research of HCQ treatment in COVID-19.

Conclusion Visualization knowledge map analysis regarding HCQ clinical treatment over the past 30 years suggested scientists are mainly focused on the autoimmune diseases therapy by HCQ. HCQ research have significantly increased since the end of 2019. Obviously, studies on HCQ in COVID-19 may lead the future direction of this field in recent years. The present study provides valuable information on HCQ research through bibliometric analysis so that researchers may identify new perspective and fields.

1. Introduction

With the widespread of syndrome coronavirus 2 (SARS-CoV-2) all over the world, hydroxychloroquine (HCQ) once again entered the public's attention for its potential therapeutic role for COVID-19 [1-3]. HCQ, an antimalarial drug, was first introduced in 1955 and quickly became favored to treat rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other chronic inflammatory diseases [4,5]. Additionally, HCQ has been reported to play an important role in the treatment of amebiasis, HIV/AIDS, and some cancers due to its immunomodulatory activity [6-8]. Previously, the publications on HCQ treatment are most articles and reviews which concentrated on the efficacy and safety. However, so far, there are hardly any reports on the systematic bibliometric analysis of HCQ research status.

Bibliometrics emerged as a statistical and quantitative analytical method in 1969 to investigate the characteristics and developments in a research field [9,10]. Nowadays, different kinds of bibliometric methods have been developed to evaluate the process and frontiers of research fields [11]. Among them,

CiteSpace software invented by Professor Chen Chaomei has been widely used as a visual bibliometric analysis in the medical field with lots of significant publications [12-14]. It is an effective analysis tool of knowledge mapping combines theories and methods from mathematics, graphics, statistics and other disciplines to reveal the core structure, developmental history, hotspots, and integral knowledge architecture of a field [15,16]. CiteSpace supports various types of bibliometric studies, including collaboration network analysis, co-word analysis, author co-citation analysis and document co-citation [17,18]. Until now, it has been continuously developed to meet the needs for visual analytic tasks and widely used in bibliometric analysis.

Our study was based on CiteSpace software to assess the core structure and hotspots of HCQ treatment research from 1991 to 2020. Besides, since COVID-19 has dramatically changed the world from December 2019, we have analyzed the related research publications and made a tiny bibliometrics analysis in order to identify the emerging trends and characteristics of HCQ in COVID-19 research.

2. Methods

2.1 Data source and strategy

We gathered the documents in Web of Science Core Collection (WOSCC) with the topic 'HCQ treatment' from 1991 to 2020. 'Article' or 'review' was selected for an in-depth analysis without language restriction. All the information about the papers was downloaded in a TXT format. After removing duplication, a total of 2642 relevant publications were obtained until the latest data on September 25th, 2020. We further searched "hydroxychloroquine" with "COVID-19" and "hydroxychloroquine" with "coronavirus" in WOS from 1991 to 2020.

2.2 Analytical strategy and tools

CiteSpace software was applied in our research to make bibliometric analysis through visualization knowledge maps. First, all of 2642 articles and reviews were imported into CiteSpace 5.7.R1 to study cooperation network of countries, keyword co-occurrence, and capture keywords with strong citation bursts. The lengths of time slicing were set from 1991 to 2020 and the years per slice was one. Threshold was set to top 30. Nodetypes represent the analysis elements, containing country, organization, author, co-citation literature, and keywords [19]. According to different kind of analysis, we adjusted the parameter settings and selected the correct nodes each time.

3. Results

3.1 General publications and trend

Thirty-year trend analysis showed that there is a general increase in the published articles and reviews on HCQ treatment from 1991 to 2020, especially in recent 10 years (Figure1A). Regarding the contribution countries, there were 51 countries in total (Figure1B). Among them, the United States has obviously

played a leading role in HCQ treatment research, with 785 papers published. The other top 10 countries are France (271), China (209), England (179), Italy (173), Germany (155), Canada (116), Spain (112), Netherlands (105) and India (100). Moreover, we picked the science citation index publications from all the documents and used bibliometrics online analysis platform to detect the distributions and cooperations on countries/regions. It found consistently that USA, France, China, UK and Italy ranked the top 5 countries (Figure 1C). It also showed there was a most frequent international cooperation between the United States and China, followed by the US and England. Dual-map overlays in CiteSpace act as citation links in visualization from a global citing base map to a global cited base map [19-21]. Different color of a link represents different source of the discipline and the labels show the subject covered by journals [22]. Furthermore, the vertical and the horizontal axes of ellipses represent the number of articles and authors around the labels [23]. There were three main citation paths in the middle of the dual-map. As the left and right sides respectively represent the map of citing and cited journals maps, the orange path indicated journals in the area labeled 'molecule/biology/immunology' were mostly cited by the publications in the 'molecule/biology/genetics' area. The other two green paths suggested all publications in 'medicine/medical/clinical' areas were respectively cited in the journals of 'health/nursing/medicine' and 'molecule/biology/genetics'.

3.2 Analysis of HCQ research areas in recent 30 years

3.2.1 Analysis of keywords co-occurrence

Keywords which definitely summarize and condense the whole content reflect the most important information of a document [24]. Therefore, the keywords of an article are often used to explore and identify hotspot in a research field [25]. Under the condition we have set in CiteSpace, the node type was selected for "keyword," the threshold was set to top 30, and 'pathfinder and pruning the merged work' were set as the pruning, which finally generated a map of keyword co-occurrence related to HCQ treatment. Nodes size reflects the number of publications or keywords frequency. Thus, the bigger the circle node, the more original articles the keyword involved. In our knowledge map, we constructed a network with 247 nodes and 377 links (Figure2A). The top 15 high-frequency keywords were hydroxychloroquine, treatment, rheumatoid arthritis, chloroquine, systemic lupus erythematosus, COVID-19, double blind, disease, methotrexate, efficacy, risk, sars-cov-2, autophagy, disease activity and coronavirus (Table1).

3.2.2 Time trends for the keywords of HCQ treatment studies

Time zone view comprised of keywords nodes showed the general evolution of research over time [26]. The more articles during that period, the more important influential the research results are [19]. Through the visualization analysis, HCQ treatment has already been a research hotspot in 1991 and was widely studied in rheumatoid arthritis, systemic lupus erythematosus and other autoimmune diseases since 1992 (Figure 2B). With the outburst of COVID-19 pandemic at the end of 2019, HCQ have become a hotspot of research.

3.2.3 Keyword clusters revealed by CiteSpace

The keywords clustering map can provide insight into the main research topics in the intellectual base [27]. In order to study the basic knowledge structure of HCQ research field, we used CiteSpace as a method for classifying information according to the similarity of literature research content. In CiteSpace project, we adopted LLR algorithm to conduct the cluster analysis. Generally, modularity Q values larger than 0.3 ($Q > 0.3$) are considered as significant cluster, and a mean silhouette value which is greater than 0.5 ($S > 0.5$) indicates that publications within a cluster contain highly consistent or similar content. The number of publications included decreases from top to bottom [19]. Totally, there are 14 major keyword clusters (0#-13#) identified in our clustering map, with the labels extracted from keywords in the publications (Figure 3A). Most of the citation keywords in clusters were concentrated from 1998 to 2017. Clustering analysis showed cluster 0# ranked first was represented as 'COVID-19', containing 30 keywords with a mean silhouette value of 0.963. Cluster1# "sulfasalazine" was the second largest cluster including 25 frequencies, followed by cluster2# 'gold sodium thiomalate'. The other clusters with relevant labels were explicitly listed in Table 2. Significantly, almost all the clusters were heavily intertwined, except for the cluster 8# and 10#. Cluster 8# centred on 'autophagy' mainly focused on the role and mechanism of HCQ in diseases. Thus, it has been demonstrated that HCQ was the only clinically-approved autophagy inhibitor, and widely studied in cancer experiments and clinical trials [28,29]. According to a high centrality value of cluster 10#, 'COVID-19' related research has definitely become a novel and urgent research hotspot.

Timeline view represents temporal characteristics of the research areas classified by clustering [19]. The knowledge map clearly shows number of nodes in chronological order from left to right on a horizontal line in each cluster. All cluster labels are arranged on the right listed from top to bottom gradually. Time span was from 1991 to 2020, with newer articles placing closer to the right side. Keywords notes with purple circles usually serve as a pivotal step to connect with each cluster. As Figure 3B showed, the nodes on the horizontal line of cluster 0#, 3#, 6#, 7# and 10# are much more and bigger, indicating these areas are very important for more studies at the corresponding time. Especially, there were plenty of purple circles in cluster 0# which suggested scientists have made many remarkable achievements in HCQ field from 1991 to 1995. In addition, high frequency keywords in cluster 9# showed chloroquine and hydroxychloroquine, which shared the similar chemical structures of quinine [30], have always been explored in comparison with the therapeutic effect, mechanism and side reaction.

3.2.4 Burst detection of keywords

In order to analyze the research hotspots shifts from 1991 to 2020, we used CiteSpace to detect the strongest burst keywords identified as indicators of the research frontier topics (Figure3C). The map shows the years when hot keywords began to appear and ended. Blue line on burst knowledge map represents time intervals, and the period of keywords bursts is showed with red line. We have totally detected the top 25 strongest citation burst words of HCQ treatment in diseases. From the burst detection analysis, methotrexate (strength: 30.7304) was the most strength burst keyword in this field during the

entire time period from 1996 to 2009, followed by sulfasalazine (22.1668), combination therapy (21.3015), toxicity (19.1906) and placebo (16.302).

3.3 Analysis of hydroxychloroquine in COVID-19 research

As a novel coronavirus epidemic broke out in China and quickly swept the world at the end of 2019, many researchers begin to focus on the role of hydroxychloroquine in COVID-19 treatment. Based on this research condition, we gathered the number of 568 articles and reviews from WOSCC, including 355 papers in Science Citation Index Expanded. Figure 4A showed the distribution of countries/regions and institutions of all the publications. Through the statistics of CiteSpace, there were mainly 38 countries involved in the study on HCQ treatment in COVID-19. The top10 country analysis indicated that the United States (183) had still been the largest contributor to this area, India (74), Italy (69), China (45), France (41), England (33) and Brazil (26) were followed. Differently, the data of SCI publications showed the USA (96), Italy (41), China (36), India (28), and France (21) were ranked in the top five (Figure 4B). Top 5 research institutions ordered by the publications from WOSCC included Aix Marseille Univ (14), Univ Tehran Med Sci (11), Univ Paris (8), Harvard Med Sch (8) and Huazhong Univ Sci & Technol (8) according to the CiteSpace analysis (Figure 4C). Besides, NEW ENGL J MED was the most frequent cited journal with 389 times, LANCET was cited 369 times and INT J ANTIMICROB AG was cited 354 times, the others were listed clearly in Figure 4D. Results of the dual-map overlays proved authoritative research on HCQ treatment in COVID-19 is already underway, covered by authority journals such as LANCET (Figure 4E). Citing journals of the 568 publications are mainly from the fields of neurology, ophthalmology, medical clinical, medicine, molecular and immunology. The cited journals are almost from the fields of health, nursing, medicine, molecular, biology and genetics. Especially, the molecular field was most concentrated in the cited journals shown in the center of the circle on the right (Figure 4E).

4. Discussion

The present study has analyzed the research characteristics and progress on HCQ treatment from 1991 to 2020 by a novel visual scientometric tool. We innovatively explored HCQ research from a bibliometric perspective and extend the application range of bibliometric analysis. Additionally, this is a novel design to investigate the study characteristics and status of COVID-19 treated with HCQ by bibliometric analysis. The research output related to HCQ treatment from 1991 to 2020 was totally 2642 after eliminating duplication. Generally, there is an upward trend in the number of publications since 2013, suggesting that HCQ has already become a popular subject with growing studies and. Significantly, the number of publications rose almost a straight line from the end of 2019 due to the spread of COVID-19 outbreak. It explained that the study on HCQ treatment in COVID-19 received increased attention from scientists through performing more and more research papers. According to the 2,642 publications we analyzed, research achievements of the USA accounted for 29.67%, followed by France (10.24%) and China (7.90%). This results were in accordance with the SCI publications we have selected among the papers from WOSCC (Figure1C). As the quantity of publications in academic journals reflected an important output of scientific research development [17], it suggested that USA, France and China are leading the

way in HCQ treatment research. Especially, the USA seems to have superior conditions for HCQ research, with plenty of research fund, advanced equipment and professional scientists [31].

Research hotspots are the scientific issues or topics demonstrated in papers which often show the development of contemporary discipline [32]. Since an article reflects its soul and essence in the form of keywords, we investigated keywords mappings to detect the topical subject, the research hotspots and the frontier transitions in HCQ knowledge domain. Regarding the high-frequency keywords in research papers from 1991 to 2020, we proved most publications were closely related to autoimmune diseases treated by HCQ, like SLE, RA and sicca syndrome. It definitely consisted with the reports that HCQ is one of the most typically used drugs to treat autoimmune related diseases [33-35]. The other high-frequency keywords such as 'double blind', 'efficacy' and 'risk' indicated the potential side effects trail are always a common accompaniment to the development of HCQ treatment. Moreover, 'coronavirus', 'COVID-19' and 'sars-cov-2' showed the research hotspots are intrinsically based on the special necessary of human health. Collectively, we see that the studies on HCQ treatment have become increasingly detailed, diverse, and systematic.

To provide more bibliometrics analysis of HCQ treatment research, the keywords of all documents were classified into fourteen categories via CiteSpaces (Figure 3A). The quality of classification and statistics data were acceptable and reliable, for the proper modularity Q values 0.75 (>0.3) and mean silhouette value 0.7966 (>0.5). We deduced from the clustering map and timeline view that the research on HCQ treatment in autoimmune diseases has already been paid much attention since 30 years ago (cluster 0#-4#, and 12#) [36,37]. Nowadays, HCQ which was regarded as a potential antiviral drug for sars-cov2 leads to not only an argument but also a new hotspot with large number of research publications (cluster 10#). Accompanied with HCQ application in clinical, the research on combination therapy of HCQ and other drugs became as another popular attention (cluster 6#). Furthermore, it reported that HCQ treatment may cause various side effects, including skin diseases, retinopathy, retinal toxicity [38-40]. We also proved the drug adverse reaction research on HCQ was absolutely an important and immortal point both in the past and at present (cluster 5#, 7#, 8#,14#). After all, drug safety is the subject of heightened concern by people all over the world.

Bursts of keywords provide a reasonable forecasting in response to the research frontier [19]. According to the strongest bursts map, it is generally in accordance with the research frontier analyzed by the keywords co-occurrence and clustering map in HCQ treatment, which indicated that our research is credible and significant. Specially, the bursts map points out a duration of the hot-topic. As the three strongest frequency words showed drug combination research of HCQ in autoimmune diseases became a hotspot from 1993 to 2009, with the strong burst words of 'combination therapy' 'methotrexate' and 'sulfasalazine'. However, we thought there was a limitation in the keyword burst detection for a lack of HCQ in COVID-19 treatment. Probably, it is due to the study on coronavirus began at the end of 2019 and was still in progress, the spacing interval is not enough for CiteSpace to calculate.

Recently, COVID-19 is absolutely to be a global health event since the 21st century [41]. The role of HCQ in COVID-19 therapy claimed by president Trump in the U.S. pushed it further into the limelight. Our analysis proved HCQ treatment in COVID-19 has definitely become a popular academic hotspot. USA, India, Italy, China and France are the top five research countries in COVID-19 treated with HCQ, which are all the countries with more severe outbreaks or strong scientific research ability. Compared with the results in SCI research documents, Italy and China are ranked before India, suggesting the quality of these countries papers may be more comprehensive and authoritative. We further found the HCQ study in COVID-19 therapy is mainly focused on the areas of medicine and biology, and has some relation with sports and rehabilitation. Considering the research on COVID-19 just started, there will be many other disciplines and fields involved for the in-depth study on the clinical treatment of HCQ in future.

Despite WHO has declared the solidarity trial including hydroxychloroquine had little or no effect on mortality, initiation of ventilation and duration of hospital stay in patients on 16th October 2020, HCQ still has received with public and researchers' concerns. Consistently, Boulware et al. reported HCQ didn't play an obvious preventive effect in people with high-risk or moderate-risk exposure to COVID-19 [42]. Rosenberg et al. indicated there was no significantly differences in in-hospital mortality of patients who treated with HCQ, azithromycin, or combination, compared with neither treatment [43]. Regarding to the bibliometrics perspective, along with the authoritative declaration that HCQ are not an effective drug for fighting with COVID-19, we speculated the research on HCQ treatment in COVID-19 might be gradually less concerned. However, the impact, therapy and safety study of HCQ in COVID-19 patients with SLE or RA will probably become new hotspot frontiers [44-46].

Our study has analyzed and summarized the research on HCQ treatment in diseases from 1991 to 2020 by bibliometric method, wishing provide new perspective of HCQ for researchers and the public. However, two limitations still exist in our research. First, all documents we gathered were only from WOSCC, which may result in several related papers lost. Second, with the development of scientific research, the articles studied on HCQ treatment in diseases are updated frequently, especially the papers on COVID-19. Thus, we might miss several recent papers.

5. Conclusion

We applied CiteSpace which served as a novel bibliometric tool to reveal scientific productivity, collaboration, and research hotspots for HCQ treatment in diseases. Until now, the USA, France and China are the lead countries in HCQ treatment research. The role and treatment of HCQ in autoimmune diseases continue to be a research hotspot. Furthermore, the study on HCQ in COVID-19 treatment is indeed a burst research topic with the urgent need of clinical treatment for the epidemic crisis.

Abbreviations

Hydroxychloroquine HCQ

Web of Science Core Collection WOSCC

systemic lupus erythematosus SLE

rheumatoid arthritis RA

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors confirm that there are no conflicts of interest.

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Author contributions

Dr. Lingjun Kong designed and performed the study. Analysis from a clinical perspective was under the guidance of Professor Wen Zhang. They received no compensation for this role.

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Tables

Table 1. Top 10 high frequency keywords in research of HCQ clinical treatment, 1991-2020.

Ranking	Keywords	Frequency	Ranking	Keywords	Frequency
1	Hydroxychloroquine	1003	6	Methotrexate	238
2	Rheumatoid arthriti	426	7	Double blind	228
3	Systemic lupus erythematosus	355	8	Disease	218
4	Chloroquine	330	9	Efficacy	152
5	Therapy	325	10	Disease activity	135

Table 2. The analysis of keywords clusters in research of HCQ clinical treatment, 1991-2020.

Cluster ID	Size	Mean	Year	Cluster label
0	30	0.963	2000	covid-19
1	25	0.837	1999	sulfasalazine
2	24	0.872	1999	gold sodium thiomalate
3	20	0.826	2001	bromocriptine
4	18	0.850	2004	tropheryma whipplei
5	17	0.763	2004	cigarette smoking
6	17	0.95	1994	gold
7	15	0.981	1999	biologics
8	15	0.920	2009	autophagy
9	14	0.966	2000	chloroquine
10	13	1	2017	covid-19
11	13	0.927	2003	classification
12	12	0.975	1999	childhood rheumatic disease
13	12	0.917	1998	colour vision

Figures

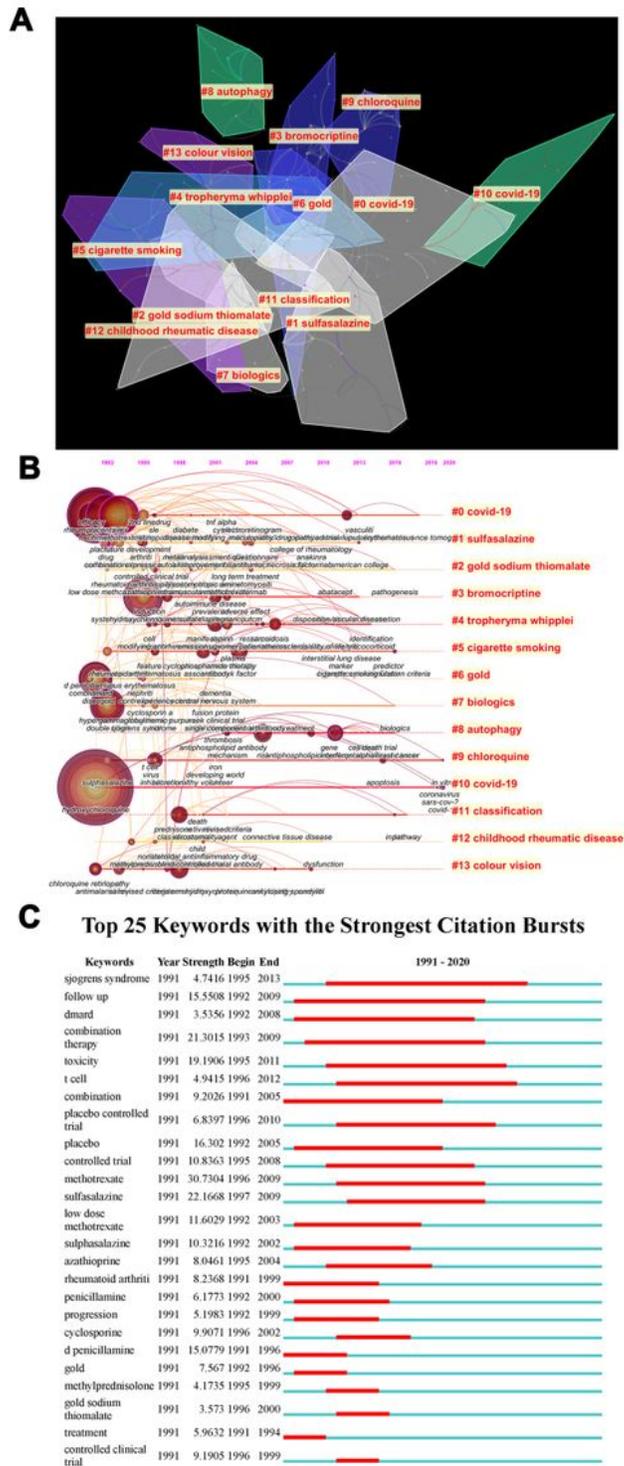


Figure 2

Hotspots and trajectories of relevant research on HCQ shown in the visual knowledge map. (A) Keywords co-occurrence map of HCQ treatment study from 1991 to 2020. (B) Time zone visualization from 1991 to 2020 is shown, some nodes are labeled with the keywords of publications.

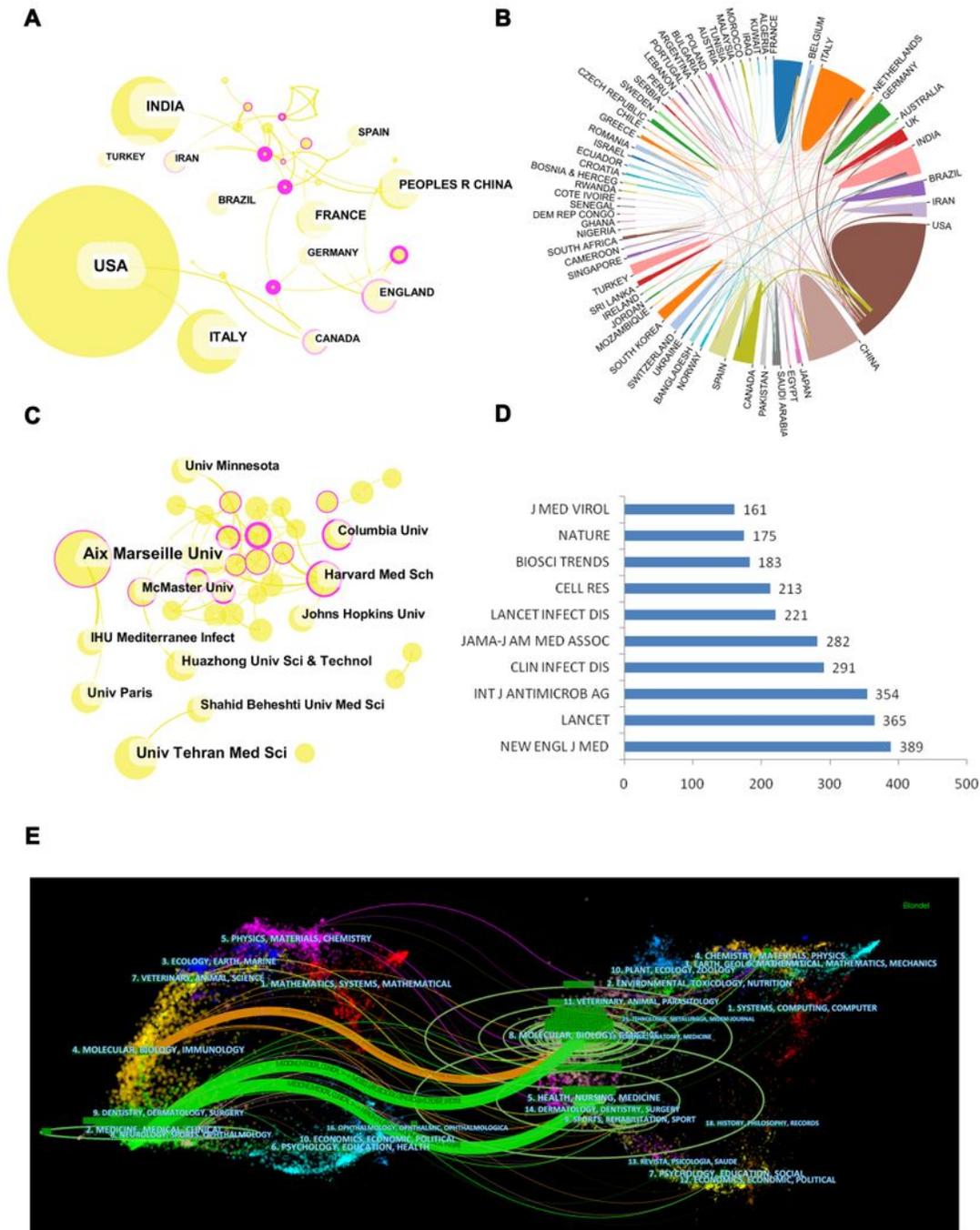


Figure 3

Clusters and bursts knowledge maps of keywords on HCQ research published from 1991 to 2020. (A) Clusters and bursts knowledge maps of co-occurrence keywords on HCQ treatment study. (B) Timeline visualization of keywords with HCQ relevant publications. (C) The keywords with the strong citation bursts in articles related to HCQ therapy.

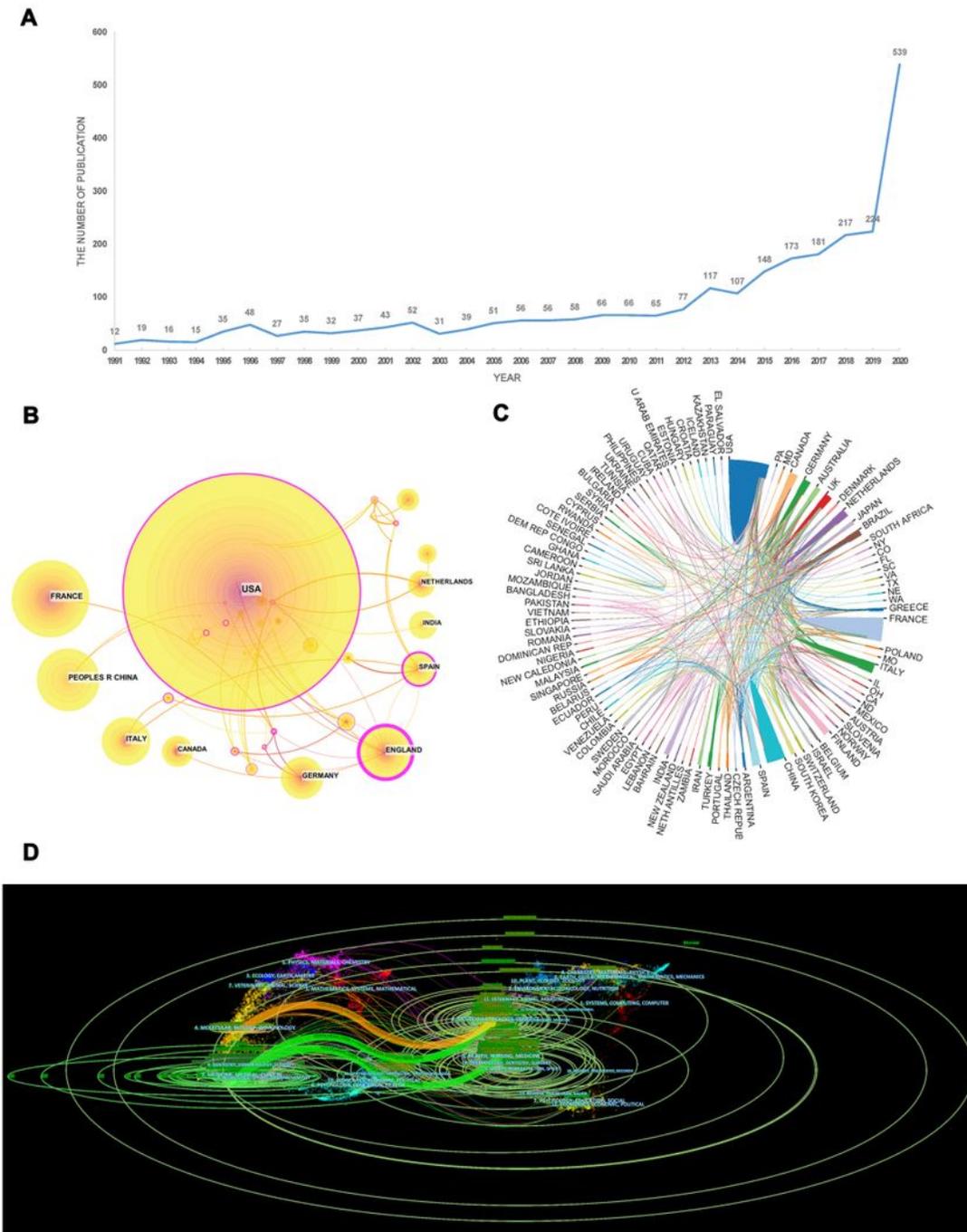


Figure 4

The bibliometric analysis of HCQ treatment in COVID-19 from 1991 to 2020. (A) (B) The academic cooperation network between countries/regions was respectively from the publications of WOSCC and SCI. (C) The cooperation of institutions was obtained through analysis of publications from WOSCC. (D) The top 10 journals with the highest citations. (E) Dual-map overlays of research on HCQ treatment in COVID-19.