



## 13 Abstract

14 The Coronavirus 2019 (COVID-19) pandemic has caused worldwide concern and has become  
15 a major medical problem. Vaccines and therapeutics are important interventions for the  
16 management of this outbreak. This study aims to use bibliometric methods to identify  
17 research trends in the domain of therapeutics and vaccines to cure patients with COVID-19  
18 since the beginning of the pandemic.

19 The Web of Science Core Collection database was retrieved for articles on therapeutic  
20 approaches to coronavirus disease management published between January 1, 2020 and May  
21 20, 2020. Identified and analyzed the data included title, corresponding author, language,  
22 publication time, publication type, research focus.

23 A total of 1569 articles on coronavirus therapeutic means from 84 countries were published in  
24 620 journals. We note the remarkable progressive increase in the number of publications  
25 related to research on therapies and vaccines for COVID-19. The United States provided the  
26 largest number of articles (405), followed by China (364). Journal of Medical Virology  
27 published most of them (n=40). 1005 (64.05%) were articles, 286 (18.23%) were letters, 230  
28 (14.66%) were reviews. The terms "COVID- 19" or "SARS-CoV-2" or "Coronavirus" or  
29 "hydroxychloroquine" or "chloroquine" or "2019-nCoV" or "ACE2" or "treatment" or  
30 "remdesivir" or "pneumonia" were most frequently used, as shown in the density visualization  
31 map. A network analysis based on keyword co-occurrence revealed five distinct types of  
32 studies: clinical, biological, epidemiological, pandemic management, and therapeutics  
33 (vaccines and treatments).

34 COVID-19 is a major disease that has had an impact on international public health at the  
35 global level. Several avenues for treatment and vaccines have been explored. Most of them  
36 focus on older drugs used to treat other diseases that have been effective for other types of  
37 coronaviruses. There is a discrepancy in the results obtained from the studies of the drugs

38 included in this study. Randomized clinical trials are needed to evaluate older drugs and  
39 develop new treatment options.

40

41 Keywords: Bibliometric analysis; Coronavirus diseases; COVID-19; Treatment; Vaccine;  
42 drug.

43

44

## 45 **Introduction**

46 The world has been facing the emergence of a new respiratory disease in Wuhan,  
47 China, since December 31, 2019. A few days later, Chinese scientists identified the causative  
48 virus, as novel coronavirus[1], and was subsequently named SARS-CoV-2 by the  
49 *Coronaviridae* Study Group (CSG) of the International Committee on Taxonomy of  
50 Viruses[2]. Since, global efforts focused on fighting Coronavirus disease 2019 (COVID-  
51 2019) pandemic. The high infectiousness of the virus posed a problem in countries where  
52 barrier measures were not being met and health care facilities became overcrowded and  
53 unable to accommodate the excess of patients. Up to now, the world health organization  
54 (WHO) and United States Centers for Disease Control and Prevention (CDC) guidelines for  
55 the management of COVID-19 have been limited to infection control and symptomatic  
56 management of patients[3,4]. There are no specific antiviral drugs or vaccines available for  
57 coronavirus. Doctors use different antiviral, antibiotic and anti-inflammatory agents based on  
58 expert opinion, case series and prospective and randomized trials conducted worldwide to  
59 relieve infected patients. It is against this background that we have referred to highlight the  
60 various treatments that have had a considerable impact on the reduction and, in particular, the  
61 spread of this pandemic throughout the world since its emergence.

62

## 63     **Methods**

### 64             **Sources of Data and Search Strategy**

65     All data were retrieved from all available journals of the Thomson Reuters Web of  
66     Knowledge on May 20, 2020 using the following search terms: (Treatment OR Vaccine)  
67     AND (COVID-19). The Web of Science provides comprehensive publication data and is the  
68     widely accepted and frequently used database for the analysis of scientific publications. The  
69     publication period considered in this study was from January 1, 2020 to May 20, 2020; a total  
70     of 4,330 articles were identified. All articles with focus on the treatment of the COVID-19  
71     and published in 2020 were included. All age groups were included. Articles related to *Severe*  
72     *acute respiratory syndrome coronavirus* (SARS-CoV or SARS-CoV-1) or *Middle East*  
73     *respiratory syndrome-coronavirus* (MERS-CoV) were excluded. Moreover, articles focusing  
74     on the infection or physiopathology of the COVID-19 were excluded. Thus, a total of 1,569  
75     articles were ultimately included in the final analyses after duplicated removed.

### 76             **Data Analysis**

77     Publications were stratified and systematically assessed according to publication days,  
78     country, journal, and authors. Additionally, the frequencies of keywords extracted from the  
79     articles were assessed and then included in a network analysis. All data were downloaded  
80     from the Web of Science and imported into VOSviewer v.1.6.15 (Centre for Science and  
81     Technology Studies, Leiden University, Leiden, The Netherlands), which is commonly used  
82     to analyze and visualize relationships among authors, countries, co-citations, and the terms  
83     used in articles [5,6]. The visualization of similarities (VOS) mapping method was used to  
84     estimate similarity (affinity) according to association strength, where higher association  
85     strength is indicative of greater similarity between terms, and a larger number of publications  
86     in which two items co-occur indicates that the terms are more closely similar to each other.

87 The number of clusters can be varied depending on threshold of similarity between the nodes.  
 88 The resolution of clustering was set as the default value (1.00) in this study[5].  
 89 Additionally, keywords were analyzed to identify popular topics in research on treatments and  
 90 vaccine to control COVID-19. Keywords indicate article research themes; co-occurring  
 91 keywords reveal associations in underlying themes among articles. The VOS method was  
 92 applied to cluster keywords into different groups; each cluster was identified with a different  
 93 color. Each keyword is represented by a circle, the diameter and label size of which denote  
 94 the number of occurrences. Colors represent groups of linked terms; the label size of a term  
 95 represents the number of publications on acupuncture for pain control in which it is used, and  
 96 the distance between two terms represents the degree to which they are associated.

97

## 98 **Results**

### 99 **General information**

100 The initial search yielded 4,330 preliminary results. After verifying the titles and abstracts of  
 101 the articles obtained from these results and removed duplicated, we retained 1,569 articles that  
 102 met our inclusion criteria (Figure 1). Types of retrieved documents are listed in Table 1.  
 103 Original research articles (1,005; 64.05%) were the main type. A total of 12 different  
 104 languages were encountered in the retrieved documents. English language (1,453; 92.61%)  
 105 and Chinese (83; 5.29%) was most encountered languages Table 2. Figure 2 presents the  
 106 distribution of publications on vaccine and treatment related to COVID-19 during the period  
 107 of January 1–May 20, 2020. Since the first publication on 30 January, an average of 14  
 108 publications has been recorded each day.

Of the 620 journals that were identified in the present study, *Journal of Medical Virology* published the most articles (40; 2.55%), followed by the *The New England Journal of Medicine* (27; 1.72%) and *International Journal of Antimicrobial Agents* (24; 1.53%) and *Nature* (24; 1.53%) (Table 3).

### Geographical distribution of retrieved publications

Eighty-four countries have contributed to the search for therapeutics and vaccines to cure patients with COVID-19. Geographical distribution of retrieved publications was presented in world map using Microsoft Excel for Microsoft 365 MSO (version 16.0.12730.20144) (Figure 3). Top countries that participated in publishing documents on the therapeutics and vaccines to cure patients with COVID-19 were listed in Table 4. The United States of America (USA) was the most productive country in this field with 407 publications, followed by China 364 publications. The USA and China participated in half (49.47%) of worldwide productivity. Moreover, these gains are concentrated in countries with higher GDP and higher rate of patient's death from COVID-19. Analysis of country coauthorships using VOSviewer showed a map with four clusters (Figure 4). Countries in the same cluster have higher collaboration than those distantly located in other clusters. Furthermore, countries with higher number of coauthorships had higher number of articles published on international collaboration. International cooperation analysis shows that the most frequent cooperation occurs in the United States and China (Figure 4).

### Profiling of authors

Of all 7,374 authors included in this subject, 774 authors published more than 2 papers and 17 authors published more than 5 papers. Table 5 shows the top 15 authors, according to the author lists of the articles included in the present study. Author's analysis showed that 58 authors appeared more than 4 times (out of 7374 authors); these authors were classified into

21 clusters with 7 clusters with at least 3 authors. The most productive authors were clustered together in cluster numbers 1 and 2 mainly (Figure 5).

### Analysis of keywords

In this section, we investigated the keywords used in the therapeutic management of COVID-19 to discover the hotspot of this topic.

The counting of author keywords revealed that the most frequent treatment used as keywords were hydroxychloroquine (n = 78 repeats), followed by chloroquine (n = 56 repeats), remdesivir (n = 31 repeats), tocilizumab (n = 22 repeats), and azithromycin (n = 20 repeats).

To visualize the connection network between author keywords, we considered only keywords with at least 10 cooccurrences and found out that 38 of 1842 keywords were entered into the network and clustered into 4 groups (Figure 6).

Cluster 1 (red) related to the “coronavirus diseases and its clinical issues”, including terms related to coronavirus, diseases complication and treatment.

Cluster 2 (green) could be called “disease epidemiology”, and includes terms like 2019-nCoV, MERS-CoV, SARS-CoV, novel coronavirus, pneumonia, outbreak, vaccine, and traditional Chinese medicine. This cluster contains 2 major topics: a) the main term “the disease” which in addition to the above-mentioned terms, but also b) “treatment and vaccine” which contains terms like vaccine, traditional Chinese medicine, and antiviral.

Cluster 3 (blue) related to “COVID-19 drug treatment”, with terms like coronavirus diseases 2019, pandemic, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and remdesivir.

Cluster 4 (yellow) with terms including drugs, MERS, SARS and therapy.

Similarly, the counting of keywords Plus revealed that the most cooccurrence drugs in the therapeutic management of COVID-19 documents are hydroxychloroquine (n = 49 repeats) and chloroquine (n = 45 repeats).

To visualize the connection network between author keywords, we considered only keywords with at least 10 cooccurrences and found out that 73 of 871 keywords were entered into the network and clustered into 4 groups (Figure 7).

Cluster 1 (red) related to the “The virus and its biology”, including terms related to SARS virus and their biology. Within this cluster, we found the topic of “virus biology”, which included terms like glycoproteins, antibodies, viral structure, and viral replication.

Cluster 2 (green) relates to “The virus and pandemic management”, and include topics related to coronavirus and to pandemic, the disease outbreak and treatment management. Within this cluster, we found the topic of “care management”, which included terms on practice guidelines and clinical laboratory techniques. Further, within this cluster, we found the topic of “treatment management”, which included terms like viral vaccine, related to Chinese traditional medicine, and drug development.

Cluster 3 (blue) related to “drug treatment”, with terms like antiviral agents, chloroquine, hydroxychloroquine, lopinavir, ritonavir, drug repositioning, drug discovery and drug combinations.

Cluster 4 (yellow) related to “Clinical epidemiology”, with terms relating to age, gender, and procedures (like x-ray, CT, viral load).

### **Most Influential Literature**

Table 6 presents the 20 most cited articles in the field of therapeutic management of COVID-19. The number of citations ranged from 23 to 179, with an average citation per item of 55.6.



These top 20 documents received the most citations among all documents (1112 times which comprise almost 47.76% of all citations). These documents consisted of 10 original articles, 3 letters, 4 reviews, 2 editorial, and 1 diagnostic criteria/guidelines. All the documents were published this year between February 4, to March 20, in 15 different journals including *The Lancet* (3 documents), *BioScience Trends* (3 documents) and *Military Medical Research* (2 documents).

The highest-ranking article was written by Wang *et al.* 2020 ( $n=179$  citations until May 23, 2020)[7], followed by a paper authored by Gao *et al.*, 2020 ( $n=91$  citations until May 23, 2020)[8], Hoffmann *et al.* 2020 ( $n=87$  citations until May 23, 2020)[9] and Gautret *et al.* 2020 ( $n=85$  citations until May 23, 2020) [10].

## Discussion

This bibliometric analysis of studies on treatment and vaccine to cure COVID-19 patients published since the beginning of the pandemic revealed that the total number of articles has steadily increased significantly since April. An average of 14 papers has been published per day since the first publication. An increase in research output has also been shown in similar research related to COVID-19 [11–13].

The largest proportion of articles in this area came from developed countries, including United States, followed by China, Italy, the United Kingdom and France. These countries, excluding China, are among the five countries with the highest number of deaths from COVID-19 on 20 May 2020 (<https://covid19.who.int/>). Possible explanations for these findings may be rapid economic growth or the progress of scientific research systems in these countries. These findings were like those reported in earlier bibliometric studies [11–15],

which found that the economic growth of a country affected the quantity of research published by its researchers.

Keywords are chosen to reflect the main purpose of the entire study, in accordance with established research principles. They can provide information about the core content of an article and can also be used to identify research trends in a particular domain. Therefore, VOSviewer was used to analyze keywords from the work selected in this study that could be considered useful in organizing and prioritizing future research on treatments and vaccines to cure patients with COVID-19. A network analysis based on keyword co-occurrence revealed five distinct types of studies, namely clinical studies, biological studies, epidemiological studies, pandemic management, and studies related to vaccines and therapeutics.

The influential articles identified in this study explored several approaches to combat the new coronavirus pandemic. Guo, Yan-Rong et al In their review publish and cited more than 43 times, discussed the current treatment and scientific advances to combat the new coronavirus pandemic. Lopinavir/ritonavir, chloroquine, remdesivir (GS-5734), nafamostat, ribavirin, oseltamivir, penciclovir/ acyclovir, ganciclovir, favipiravir (T-705), and nitazoxanide have been listed as coronavirus treatment strategies, based on experience with the SARS-CoV and MERS-CoV epidemics. Rescue treatment with convalescent plasma and immunoglobulin G are delivered to some critical cases according to their conditions [16]. Russell et al 2020 [17] in a meta-analysis found that there is no clinical evidence that corticosteroids provide a net benefit in treating respiratory infections due to RSV, influenza, SARS-CoV or MERS-CoV and further conclude that corticosteroid treatment should not be used for the treatment of lung injury or shock induced by 2019-nCoV outside of a clinical trial[17]. The most widely cited article by Wang et al. 2020 [7] on 4 February, evaluated in vitro the antiviral efficacy of several FDA-approved drugs, including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, and two well-known broad-spectrum antiviral drugs, remdesivir (GS-5734) and

favipiravir (T-705) against a clinical isolate of 2019-nCoV. The authors concluded that remdesivir and chloroquine are highly effective in controlling 2019-nCoV infection in vitro[7]. The second most cited paper, by Gao et al 2020[8] on February 19, recommends, given the urgent clinical demand, chloroquine phosphate to treat COVID-19-associated pneumonia in larger populations[8]. Another in vitro study conducted in China by Yao et al 2020 [18] on March 09, 2020 and cited nearly 50 times, shows that hydroxychloroquine was more potent than chloroquine in inhibiting SARS-CoV-2 in vitro[18]. Furthermore, despite the small sample size, Gautret et al 2020 [10] showed that hydroxychloroquine treatment is significantly associated with the reduction/disappearance of viral load in COVID-19 patients and that its effect is enhanced by azithromycin[10]. The study conducted by Cao et al 2020 [19] observed no benefit with lopinavir-ritonavir treatment beyond standard care by randomizing adult in patients with severe COVID-19 in a 1:1 ratio to receive either lopinavir-ritonavir in addition to standard care or standard care alone[19]. The third most cited article authored by Hoffmann et al 2020 [9] demonstrated that SARS-CoV-2 uses ACE2 receptor for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor would block TMPRSS2 activity and might constitute a treatment option [9]

Our study has the advantage of being the first to provide a bibliometric overview of the search for therapeutic means to cure COVID-19. We have done our best to include all potential articles. Nevertheless, some limitations inherent to bibliometric analysis may be unavoidable. The database is continuously updated, and we have only selected literature from January 1, 2020 to May 20, 2020, without literature published after this date. The number of studies may increase rapidly with the breakthrough of future research. In addition, it appears that some medical journals are not indexed in Web of Sciences and therefore some articles may be missed. Some people may object to the use of Web of Sciences for data retrieval. However, we still believe that such a large amount of macroeconomic data and such a detailed analysis

of the literature are sufficient to represent the trend of development in this area of research. Finally, we believe that researchers can ignore a minute number of potentially missing publications and that our results are sufficient to represent trends in this field.

## Conclusion

In conclusion, this study used bibliometric methods to identify research trends in the domain of therapeutics and vaccines to cure patients with COVID-19. The most important findings of this study are as follows: (1) the remarkable progressive increase in the number of publications related to research on therapies and vaccines for COVID-19 (2) most of these studies were conducted in the countries with the highest number of deaths (USA, Italy, United Kingdom and France) and China, first affected country (3) most of the publications were published in the Journal Of Medical Virology followed by The New England Journal Of Medicine and the International Journal Of Antimicrobial Agents (5) the terms "COVID- 19" or "SARS-CoV-2" or "Coronavirus" or "hydroxychloroquine" or "chloroquine" or "2019-nCoV" or "ACE2" or "treatment" or "remdesivir" or "pneumonia" were most frequently used, as shown in the density visualization map (6) A network analysis based on keyword co-occurrence revealed five distinct types of studies: clinical, biological, epidemiological, pandemic management, and therapeutics (vaccines and treatments).

## Acknowledgements

None

## Funding

No funding was received for writing this study.

## Disclosure

The authors declare that they have no conflicts of interest.

## Ethics approval and consent to participate

The analysis in this study is based on a retrospective bibliometric technique; therefore, no ethical approval was required.

## References

- [1] Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. *Nature* 2020;579:265–9. <https://doi.org/10.1038/s41586-020-2008-3>.
- [2] Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020:1–9. <https://doi.org/10.1038/s41564-020-0695-z>.
- [3] Clinical management of COVID-19 n.d. <https://www.who.int/publications-detail/clinical-management-of-covid-19> (accessed May 30, 2020).
- [4] CDC. Coronavirus Disease 2019 (COVID-19). *Cent Dis Control Prev* 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html> (accessed May 30, 2020).
- [5] van Eck NJ, Waltman L. Citation-based clustering of publications using CitNetExplorer and VOSviewer. *Scientometrics* 2017;111:1053–70. <https://doi.org/10.1007/s11192-017-2300-7>.
- [6] Nj van E, L W. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 2009;84:523–38. <https://doi.org/10.1007/s11192-009-0146-3>.
- [7] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71. <https://doi.org/10.1038/s41422-020-0282-0>.
- [8] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14:72–3. <https://doi.org/10.5582/bst.2020.01047>.
- [9] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020;181:271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>.
- [10] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949. <https://doi.org/10.1016/j.ijantimicag.2020.105949>.

- [11] Chahrour M, Assi S, Bejjani M, Nasrallah AA, Salhab H, Fares M, et al. A Bibliometric Analysis of COVID-19 Research Activity: A Call for Increased Output. *Cureus* 2020;12:e7357. <https://doi.org/10.7759/cureus.7357>.
- [12] Tao Z, Zhou S, Yao R, Wen K, Da W, Meng Y, et al. COVID-19 will stimulate a new coronavirus research breakthrough: a 20-year bibliometric analysis. *Ann Transl Med* 2020;8:528. <https://doi.org/10.21037/atm.2020.04.26>.
- [13] Zhou Y, Chen L. Twenty-Year Span of Global Coronavirus Research Trends: A Bibliometric Analysis. *Int J Environ Res Public Health* 2020;17. <https://doi.org/10.3390/ijerph17093082>.
- [14] Lou J, Tian S-J, Niu S-M, Kang X-Q, Lian H-X, Zhang L-X, et al. Coronavirus disease 2019: a bibliometric analysis and review. *Eur Rev Med Pharmacol Sci* 2020;24:3411–21. [https://doi.org/10.26355/eurrev\\_202003\\_20712](https://doi.org/10.26355/eurrev_202003_20712).
- [15] Hossain MM. Current Status of Global Research on Novel Coronavirus Disease (COVID-19): A Bibliometric Analysis and Knowledge Mapping. Rochester, NY: Social Science Research Network; 2020. <https://doi.org/10.2139/ssrn.3547824>.
- [16] K D, B L, C L, H Z, T Y, J Q, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* 2020;117:9490–6. <https://doi.org/10.1073/pnas.2004168117>.
- [17] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet* 2020;395:473–5. [https://doi.org/10.1016/S0140-6736\(20\)30317-2](https://doi.org/10.1016/S0140-6736(20)30317-2).
- [18] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* n.d. <https://doi.org/10.1093/cid/ciaa237>.
- [19] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020;382:1787–99. <https://doi.org/10.1056/NEJMoa2001282>.
- [20] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 2020;395:1033–4. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- [21] Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020;7:4. <https://doi.org/10.1186/s40779-020-0233-6>.
- [22] Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Mil Med Res* 2020;7:11. <https://doi.org/10.1186/s40779-020-00240-0>.
- [23] Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020;19:149–50. <https://doi.org/10.1038/d41573-020-00016-0>.
- [24] Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends* 2020;14:69–71. <https://doi.org/10.5582/bst.2020.01020>.
- [25] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020;6:1–4. <https://doi.org/10.1038/s41421-020-0156-0>.
- [26] Lim J, Jeon S, Shin H-Y, Kim MJ, Seong YM, Lee WJ, et al. Case of the Index Patient Who Caused Tertiary Transmission of Coronavirus Disease 2019 in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Pneumonia

- Monitored by Quantitative RT-PCR. *J Korean Med Sci* 2020;35.  
<https://doi.org/10.3346/jkms.2020.35.e79>.
- [27] Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet Lond Engl* 2020;395:e30–1. [https://doi.org/10.1016/S0140-6736\(20\)30304-4](https://doi.org/10.1016/S0140-6736(20)30304-4).
- [28] Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect* 2020;9:382–5. <https://doi.org/10.1080/22221751.2020.1729069>.
- [29] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci* 2020;12:1–5. <https://doi.org/10.1038/s41368-020-0074-x>.
- [30] Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends* 2020;advpub. <https://doi.org/10.5582/bst.2020.01030>.
- [31] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther* 2020;14:58–60. <https://doi.org/10.5582/ddt.2020.01012>.
- [32] Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020. <https://doi.org/10.12932/AP-200220-0772>.

381 **Table 1: Types of retrieved documents**

Document Types	Records	% of 1569
Article	1005	64.05
Letter	286	18.23
Review	230	14.66
Editorial	153	9.75
Other	122	7.78
Early Access	73	4.65
News	47	3.00
Case Report	34	2.17
Abstract	26	1.66
Clinical Trial	4	0.26
Correction	4	0.26
Reference Material	3	0.19
Unspecified	3	0.19
Biography	2	0.13

383 **Table 2- Languages**

Languages	Records	% Of 1569
English	1453	92.61
Chinese	83	5.29
German	10	0.64
Spanish	10	0.64
French	5	0.32
Hungarian	4	0.26
Italian	3	0.19
Dutch	2	0.12
Swedish	2	0.12
Danish	1	0.06
Icelandic	1	0.06
Portuguese	1	0.06

385 **Table 3- Top 10 most productive journal**

Journal	Records	% Of 1569	Journal Impact 2018	H Index
<i>Journal of Medical Virology</i>	40	2.549 %	2.049	105
<i>The New England Journal Of Medicine</i>	27	1.721 %	37.909	933
<i>Nature</i>	24	1.530 %	43.070	1096
<i>International Journal of Antimicrobial Agents</i>	24	1.530 %	4.615	111
<i>Journal of Biomolecular Structure Dynamics</i>	23	1.466 %	3.310	58
<i>Annals of The Rheumatic Diseases</i>	22	1.402 %	14.299	212
<i>Pharmacological Research</i>	22	1.402 %	5.574	118
<i>Medical Hypotheses</i>	21	1.338 %	1.322	77
<i>BMJ Clinical Research Ed</i>	18	1.147 %	0.48	0
<i>Dermatologic Therapy</i>	15	0.956 %	1.74	60
<i>European Review For Medical And Pharmacological Sciences</i>	15	0.956 %	2.721	48
<i>Chinese Journal Of Tuberculosis And Respiratory Diseases</i>	15	0.956 %	0.340	16



386 **Table 4- Top 15 most productive countries**

iso_code	Location	Total documents	Total confirmed COVID-19 cases	Total confirmed COVID-19 deaths	Total cases per million	Total deaths per million	GDP per capita	Population
USA	United States	405	1528568	91921	4617,993	277,705	54225,446	331002647
CHN	China	364	84065	4638	58,406	3,222	15308,712	1439323774
ITA	Italy	177	226699	32169	3749,457	532,055	35220,084	60461828
GBR	United Kingdom	84	248818	35341	3665,233	520,593	39753,244	67886004
FRA	France	83	143427	28022	2197,323	429,301	38605,671	65273512
IND	India	78	106750	3303	77,355	2,393	6426,674	1380004385
DEU	Germany	64	176007	8090	2100,725	96,558	45229,245	83783945
CAN	Canada	58	79101	5912	2095,826	156,642	44017,591	37742157
AUS	Australia	51	7068	99	277,178	3,882	44648,71	25499881
IRN	Iran	42	124603	7119	1483,494	84,757	19082,62	83992953
ESP	Spain	39	232555	27888	4973,93	596,474	34272,36	46754783
CHE	Switzerland	37	30535	1613	3528,174	186,374	57410,166	8654618
BRA	Brazil	34	271628	17971	1277,892	84,546	14103,452	212559409
JPN	Japan	27	16385	771	129,55	6,096	39002,223	126476458
ISR	Israel	24	16650	277	1923,623	32,003	33132,32	8655541
OWID_WRL	World	1569	4861974	323156	623,746	41,458	15469,207	7794798729

387

388

389

390 **Table 5 - Top 12 most productive authors**

Author		Documents	h-index	Average citations per item	Sum of Times Cited	Without self citations
Jiang, Shibo	[1] Fudan Univ, Sch Basic Med Sci, Key Lab Med Mol Virol MOE NHC CAMS, Shanghai 200032, Peoples R China; [ 2 ] New York Blood Ctr, Lindsley F Kimball Res Inst, New York, NY 10065 USA	11	5	8,27	91	83
Rolain, Jean-Marc	Aix Marseille Univ, MEPHI, AP HM, IRD, IHU Mediterranee Infection, Marseille, France	11	4	14,36	158	152
Raoult, Didier	Aix Marseille Univ, MEPHI, AP HM, IRD, IHU Mediterranee Infection, Marseille, France	10	4	15,6	156	151
Colson, Philippe	Aix Marseille Univ, MEPHI, AP HM, IRD, IHU Mediterranee Infection, Marseille, France	8	4	19,5	156	152
Du, Lanying	Lindsley F. Kimball Research Institute, New York Blood Center, New York, NY, USA.	8	4	6,63	53	48
Mahase, Elisabeth	BMJ Publishing Group, British Med Assoc House, Tavistock Square, London Wc1h 9jr, England	7	1	0,43	3	2
Montecucco, Carlomaurizio	Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Lombardia, Italy.	7	1	0,33	2	2
Shi, Zhengli	Chinese Acad Sci, Wuhan Inst Virol, CAS Key Lab Special Pathogens & Biosafety, Wuhan, Peoples R China	6	5	41,5	249	245
Zhang, Wei	PLA 900th Hospital of Joint Service CorpsFuzhou, Chinaand.	6	4	7,71	54	54
Baden, Lindsey R	the <i>New England Journal of Medicine</i> (NEJM)	6	2	1,83	11	11
Rubin, Eric J	the <i>New England Journal of Medicine</i> (NEJM)	6	2	1,83	11	11
Monti, Sara	Rheumatology, Fondazione IRCCS Policlinico S. Matteo, University of Pavia, Pavia, Italy Experimental Medicine, University of Pavia, Pavia, Italy"	6	1	0,4	2	2

392 Tableau 6 – Top 20 most cited papers

Title and journal	Reference	Total Citations	Publication Date	First author institution	First author Country	Collaboration Countries	Journal Impact 2018	Document Type	Main findings
Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. <i>Cell research</i> , 30(3), 269-271.	Wang et al. [7]	179	04/02/2020	Chinese Acad Sci, Wuhan Inst Virol, Ctr Biosafety Mega Sci, State Key Lab Virol, Wuhan 430071, Peoples R China	China		17.848	Original scientific papers	Remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro.
Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. <i>Bioscience trends</i> .	Gao et al. [8]	91	29/02/2020	Qingdao Univ, Sch Pharm, Dept Pharmacol, Qingdao, Shandong, Peoples R China	China		1.686	Letter	Considering the urgent clinical demand, chloroquine phosphate is recommended to treat COVID-19 associated pneumonia in larger populations in the future
SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. <i>Cell</i> .	Hoffman et al. [9]	87	05/03/2020	Leibniz Inst Primate Res, German Primate Ctr, Infect Biol Unit, Gottingen, Germany	Germany	Austria, Russia	36.216	Original scientific papers	SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor approved for clinical use blocked entry and might constitute a treatment option. Finally, the sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry. Important commonalities between SARS-CoV-2 and SARS-CoV infection and identify a potential target for antiviral intervention.
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. <i>International journal of antimicrobial agents</i> , 105949.	Gautret et al. [10]	85	20/03/2020	IHU-Mediterranean Infection, Marseille, France; Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, Marseille, France.	France		4.615	Original scientific papers	Despite its small sample size, hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.
Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. <i>The Lancet</i> , 395(10223), 473-475.	Russell et al. [17]	82	07/02/2020	Univ Edinburgh, Ctr Inflammation Res, Queens Med Res Inst Edinburgh, Edinburgh, Midlothian, Scotland	United Kingdom		59.102	Editorial Material	Corticosteroid treatment should not be used for the treatment of 2019-nCoV-induced lung injury or shock outside of a clinical trial.
COVID-19: consider cytokine storm syndromes and immunosuppression. <i>The Lancet</i> , 395(10229), 1033-1034.	Mehta et al. [20]	68	12/03/2020	UCL, Div Med, Ctr Inflammation & Tissue Repair, UCL Resp, London, England	United Kingdom		59.102	Letter	Identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.
A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. <i>New England Journal of Medicine</i> .	Cao et al. [19]	61	18/03/2020	From the Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases	China	United Kingdom, USA	37.909	Original scientific papers	In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.

A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). <i>Military Medical Research</i> , 7(1), 4.	Jin et al. [21]	59	06/02/2020	Wuhan Univ, Zhongnan Hosp, Ctr Evidence Based & Translat Med, Wuhan 430071, Peoples R China	China		1.730	Diagnostic criteria/guidelines	This guideline includes the guideline methodology, epidemiological characteristics, disease screening and population prevention, diagnosis, treatment and control (including traditional Chinese Medicine), nosocomial infection prevention and control, and disease nursing of the 2019-nCoV. Moreover, a whole process of a successful treatment case of the severe 2019-nCoV infected pneumonia and experience and lessons of hospital rescue for 2019-nCoV infections.
In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). <i>Clinical Infectious Diseases</i> .	Yao et al. [18]	48	09/03/2020	Drug Clinical Trial Center, Peking University Third Hospital, Beijing, China.	China		9.055	Original scientific papers	Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro.
The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. <i>Military Medical Research</i> , 7(1), 1-10.	Guo et al. [22]	43	13/03/2020	Guangdong Prov Key Lab Biomed Imaging, Zhuhai 519000, Guangdong, Peoples R China	China	Singapore	1.730	Review	
Therapeutic options for the 2019 novel coronavirus (2019-nCoV).	Li et al. [23]	39	10/02/2020	Cent South Univ, Xiangya Sch Publ Hlth, Dept Epidemiol & Hlth Stat, Changsha, Peoples R China	China	Belgium	57.618	Editorial Material	
Drug treatment options for the 2019-new coronavirus (2019-nCoV). <i>Bioscience trends</i> , 14(1), 69-71.	Lu et al. [24]	38	29/02/2020	Fudan Univ, Sci Res Ctr, Shanghai Publ Hlth Clin Ctr, Shanghai, Peoples R China	China		1.686	Review	Lopinavir /Ritonavir, Nucleoside analogues, Neuraminidase inhibitors, Remdesivir, peptide (EK1), abidol, RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs (such as hormones and other molecules), Chinese traditional medicine, such as ShuFengJieDu Capsules and Lianhuaqingwen Capsule, could be the drug treatment options for 2019-nCoV. However, the efficacy and safety of these drugs for 2019-nCoV still need to be further confirmed by clinical experiments. // In general, there are no specific antiviral drugs or vaccines for 2019-nCoV. All of the drug options come from experience treating SARS, MERS or some other new influenza virus previously. Active symptomatic support remains key to treatment. These drugs above would be helpful and the efficacy needs to be further confirmed.
Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. <i>Cell discovery</i> , 6(1), 1-4.	Liu et al. [25]	35	18/03/2020	Chinese Acad Sci, State Key Lab Virol, Wuhan Inst Virol, Ctr Biosafety Mega Sci, Wuhan 430071, Peoples R China	China		4.6	Letter	HCQ can efficiently inhibit SARS-CoV-2 infection in vitro. In combination with its anti-inflammatory function, we predict that the drug has a good potential to combat the disease. This possibility awaits confirmation by clinical trials. We need to point out, although HCQ is less toxic than CQ, prolonged and overdose usage can still cause poisoning. And the relatively low SI of HCQ requires

									careful designing and conducting of clinical trials to achieve efficient and safe control of the SARS-CoV-2 infection.
Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. <i>Journal of Korean medical science</i> , 35(6).	Lim et al. [26]	34	14/02/2020	Hanyang Univ, Myongji Hosp, Coll Med, Dept Lab Med, Goyang, South Korea	South Korea		1.716	Original scientific papers	When lopinavir/ritonavir was used, they found reduced viral loads and improved clinical symptoms during the treatment. So lopinavir/ritonavir can be recommended to relatively high-risk groups of COVID-19 pneumonia (elderly patients or patients with underlying diseases) from the early stage. But they need more evidence to prove the clinical efficacy of lopinavir/ritonavir based on well controlled clinical trials.
Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. <i>Lancet (London, England)</i> , 395(10223), e30.	Richards on et al. [27]	34	04/02/2020	BenevolentAI, London, England	United Kingdom		59.102	Original scientific papers	They identified baricitinib, which is predicted to reduce the ability of the virus to infect lung cells. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or recommendation.
Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. <i>Emerging microbes &amp; infections</i> , 9(1), 382-385.	Tian et al. [28]	30	17/02/2020	MOE/NHC/CAMS Key Laboratory of Medical Molecular Virology, School of Basic Medical Sciences, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China	China		6.212	Original scientific papers	These results suggest that CR3022 has the potential to be developed as candidate therapeutics, alone or in combination with other neutralizing antibodies, for the prevention and treatment of 2019-nCoV infections. There expect more cross-reactive antibodies against 2019-nCoV and SARS-CoV or other coronaviruses to be identified soon, facilitating the development of effective antiviral therapeutics and vaccines.
High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa.. <i>International journal of oral science</i> , 12(1), 1-5.	Xu et al. [29]	27	24/02/2020	Sichuan Univ, Res Unit Oral Carcinogenesis & Management, Natl Clin Res Ctr Oral Dis, Chinese Acad Med Sci, State Key Lab Oral Dis, West, Chengdu, Sichuan, Peoples R China	China		2.75	Original scientific papers	
Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. <i>Bioscience trends</i> .	Wang et al. [30]	26	29/02/2020	Shanghai Univ Tradit Chinese Med, Yueyang Hosp Integrated Tradit Chinese & Western, Dept Resp Dis, Shanghai, Peoples R China	China		1.686	Original scientific papers	The efficacy of antiviral treatment including lopinavir/ritonavir, arbidol, and SFJDC warrants further verification in future study.
Discovering drugs to treat coronavirus disease 2019 (COVID-19). "Drug discoveries & therapeutics 14.1 (2020): 58-60.	Dong et al. [31]	23	29/02/2020	Qingdao Univ, Sch Pharm, Dept Pharmacol, Qingdao, Shandong, Peoples R China	China		1.110	Review	Several drugs such as chloroquine, arbidol, remdesivir, and favipiravir are currently undergoing clinical studies to test their efficacy and safety in the treatment of coronavirus disease 2019 (COVID-19) in China; some promising results have been achieved thus far. This article summarizes agents with potential efficacy against SARS-CoV-2. There are no finally verified antivirals specific to COVID-19 at present. The efficacy and safety of these candidate drugs in the treatment of COVID-19 need to be

Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. <i>Asian Pac J Allergy Immunol</i> , 38(1), 1-9.	Prompt chara et al. [32]	23	01/03/2020	Chulalongkorn Univ, Fac Med, Chula Vaccine Res Ctr Chula VRC, Ctr Excellence Vaccine Res & Dev, Bangkok 10330, Thailand	Thailand		1.747	Review	confirmed in further preclinical and clinical trials.
--	--------------------------	----	------------	---	----------	--	-------	--------	---

393

394

395

Figure 1: Flow chart of literature filtering included in this study.

Figure 2: Number of publications per day that explore approaches to address the emerging coronavirus pandemic between January 1 and May 20, 2020. A-Number of publications per day; B- Cumulative publication

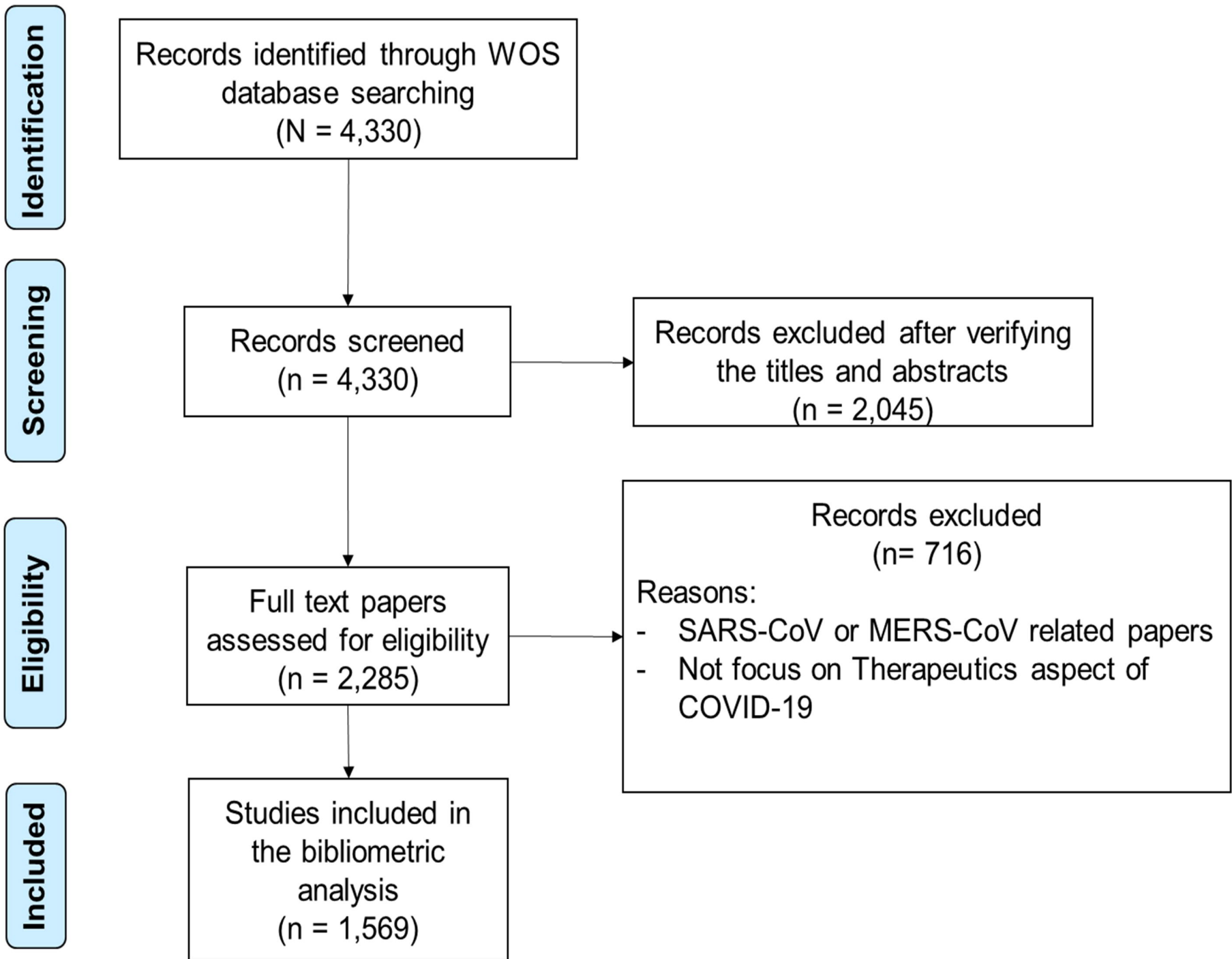
Figure 3: World maps showing the geographical distribution of retrieved publications.

Figure 4: Analysis of country co-authorships. The node's diameter is proportional to the country production. It appears that scientific publications were mainly driven by the research hubs such as the United States, China, Italy, United Kingdom, France, and India, which were also heavily hit by COVID-19.

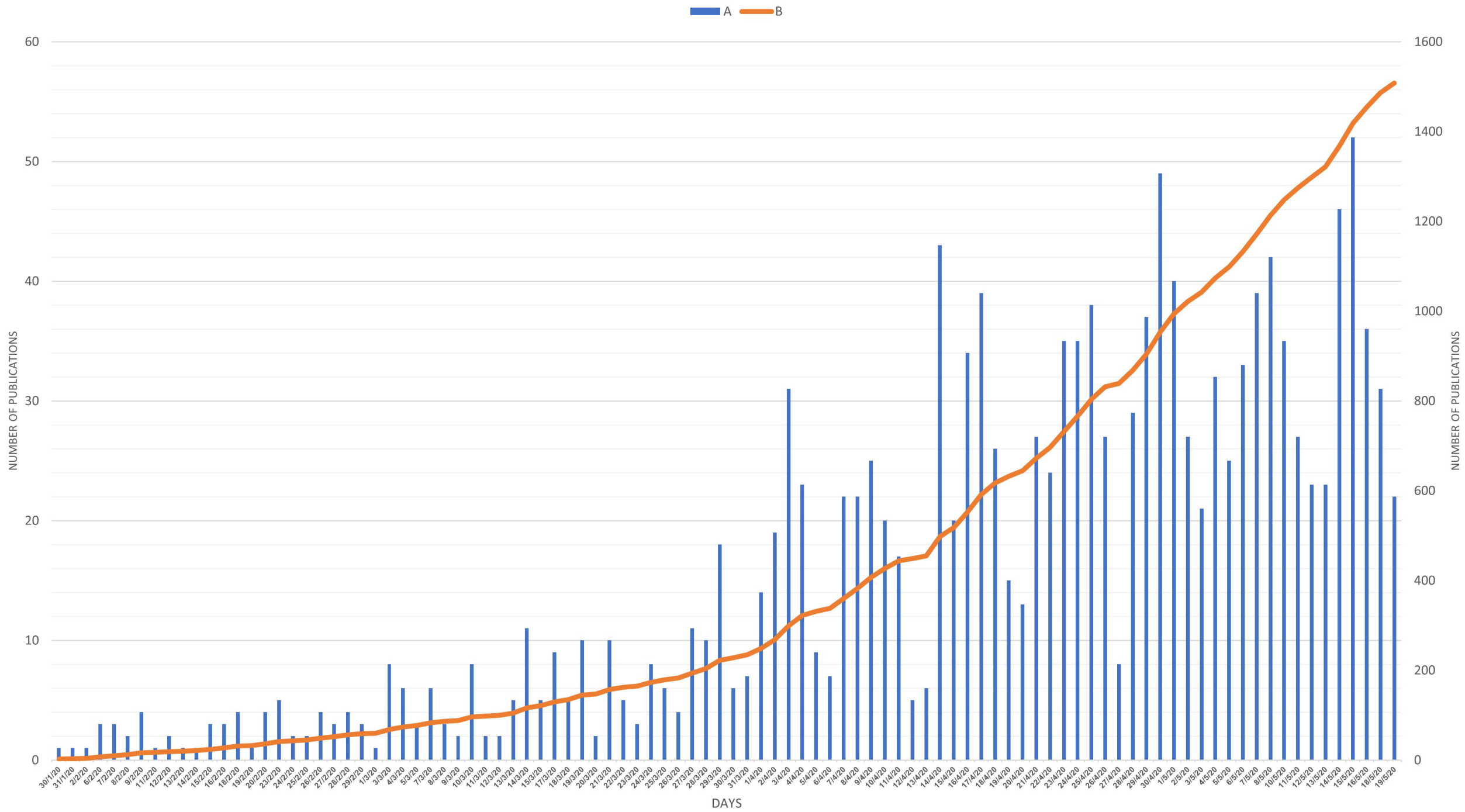
Figure 5: Network visualization map of study authors for researchers' co-authorships. A minimum of 4 yielded 58 authors. The node's diameter corresponds to the author production.

Figure 6: The connection network between author keywords with at least 10 co-occurrences. Out of 1842 keywords, 38 were entered into this network and clustered into 4 groups, which are depicted in different colors.

Figure 7. The connection network between keywords Plus with at least 10 co-occurrences. Out of 1842 keywords, 73 were entered into this network and clustered into 4 groups, which are depicted in different colors.







Série 1

405

1

