

Characteristics of Registered Systematic Reviews on Treatment for COVID-19 in Prospero Platform

Ruinian Zhang

Lanzhou University

Ya Gao

Lanzhou University

Dairong Xie

Lanzhou University

Rongna Lian

Lanzhou University

Jinhui Tian (✉ tjh996@163.com)

Key Laboratory of Evidence-based Medicine and Knowledge Translation of Gansu Province, Lanzhou University, Lanzhou, China <https://orcid.org/0000-0002-0054-2454>

Research

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Abstract

Background: Characteristics and research collaboration of registered systematic reviews (SRs) on treatment for coronavirus disease 2019 (COVID-19) remain unclear. This study aimed to analyze research collaboration, interventions, and outcome measures in registered SRs of treatment associated with COVID-19 and point out the problem.

Methods: PROSPERO was searched for SRs of treatment related to COVID-19 as of June 2, 2020. Excel 2016 was used for descriptive statistical analysis of the extracted information. VOSviewer 1.6.14 software was used to generate network maps for collaborations between countries and institutions.

Results: A total of 189 SRs were included, which were registered by 301 institutions from 39 countries. China (69, 36.50%) was the country with the highest output. Cooperation between countries was not close enough. Chengdu university of traditional Chinese medicine (7, 3.70%) was the institutions with the highest output. There is close cooperation between institutions. Interventions included antiviral therapy (81, 42.86%), respiratory support (16, 8.47%), circulation support (11, 5.82%), plasma therapy for convalescent patients (11, 5.82%), immunotherapy (9, 4.76%), TCM Treatment (9, 4.76%), rehabilitation treatment (5, 2.65%), anti-inflammatory treatment (16, 8.47%), and other treatments (31, 16.40%). In antiviral therapy (81, 42.86%), the most commonly used drugs were chloroquine/hydroxychloroquine (26, 13.76%), followed by remdesivir (12, 6.35%), lobinavir/ritonavir(11, 5.82%), favipiravir (5, 2.65%), ribavirin (5, 2.65%), interferon (5, 2.65%), abiron (4, 2.12%), abidor (4, 2.12%), but the description was brief, and no specific implementation plan was provided. The most frequently used primary outcome was mortality rate (92, 48.68%), and the most frequently used secondary outcome was length of hospital stay (48, 25.40%). The expression of the outcomes was not standardized.

Conclusions: Many COVID-19 SRs of treatment have been registered, but the completion rate was low. Although there were some collaborations between countries and institutions of the current registered SRs of treatment related to COVID-19 on PROSPERO, cooperation between countries should be further strengthened. More attention should be paid to the deficiency of interventions and outcome measures, and the standardization of results should be strengthened.

1. Introduction

In late December 2019, an outbreak of pneumonia of unknown origin characterized by strong interpersonal transmission. Then scientists found that the Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹⁻⁵ This is a coronavirus of the genus beta. It is enveloped with round or oval particles. The main clinical manifestations of COVID-19 are fever, dry cough, and fatigue. Pathological changes of lung, spleen, hilar lymph nodes, bone marrow, heart, and blood vessels are observed. The virus is generally susceptible to human infection.⁶ Within three months, it has affected six continents.^{7,8} As of August 20, 2020, 22817751 cases have been reported, including 793379 deaths.⁹

PROSPERO is an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development. After the outbreak, there was no clear and effective treatment and no specific medicine, medical workers and scientific researchers actively carry out research and have registered numerous COVID-19 treatment systematic reviews (SRs). However, no research has focused on the characteristics of these registered SRs. This study was designed to evaluate the cooperation between countries and institutions and the distribution of outcome measures in registered COVID-19 treatment SRs, to provide a reference for future researchers to register and carry out COVID-19 SRs.

2. Materials And Methods

2.1. Data sources

We systematically searched the PROSPERO registration platform (<https://www.crd.york.ac.uk/prospero>) to identify all registered COVID-19 treatment SRs. The deadline for retrieval is June 2, 2020.

2.2. Inclusion and exclusion criteria

The type of included study was registered SRs on PROSPERO. The study population was patients diagnosed with COVID-19, and there were no restrictions on age, gender, race, and course of disease. Intervention was arbitrary treatment. We excluded basic science, diagnostic tests, empirical studies, and health services. Duplicate records were also excluded.

2.3. Study selection and data extraction

Two researchers independently reviewed and screened and the retrieved records based on pre-determined inclusion and exclusion criteria, and then exchanged checks with each other. Finally, through communication with the third researcher, the dispute was resolved.

One researcher used a predefined form to extract detailed data from included registrations, while another reviewer verified the accuracy of the extracted data. Specific data include: subject, author, language, research type, discipline type, interventions, control measures, country, institution, primary and secondary outcomes, registration time and expected completion time.

2.4. Data management and analysis

We preprocess the extracted data and standardize institutions, interventions, and outcomes with different expressions. Microsoft Excel was used for descriptive analysis of the extracted data. Then, VOSviewer 1.6.14 (Leiden University, Leiden, Netherlands) software was used to evaluate the relation between countries and institutions, and generate the corresponding cooperation network diagram.¹⁰⁻¹³ In the obtained network diagram, nodes represent the elements of analysis (countries and institutions), node size reveals frequency, color of nodes indicate different clusters, and lines represent the cooperation between different nodes. The parameters of VOSviewer are as follows: counting method (fractional counting), ignoring documents with multiple authors (maximum number of authors per document is 25).

3. Results

3.1. General characteristics of registered SRs

By June 2, 2020, 205 SRs were retrieved, of which 189 met the inclusion criteria. By August 3, 2020, 122 SRs had reached the expected completion time, of which 111 SRs were still under review ongoing (90.98%), and only 11 SRs (9.02%) have been completed but have not yet been published. All details are shown in Table 1.

Among the 189 included SRs, 164 (86.77%) reported bias risk assessment methods, and the remaining 25 (13.23%) did not report. The most commonly used evaluation method was Cochrane risk of bias tool (129, 78.65%), followed by NOS (44, 26.82%), and ROBINS (12, 7.30%). In addition, 89 (47.09%) SRs did not inform the data analysis software used, and the remaining 100 (52.91%) reported. The most widely used software was review manager, with 60 (60.00%) SRs. Stata (32, 32.00%), R software (13, 13.00%) and SPSS (4, 4.00%) rank 2 to 4.

In terms of research funding sources, 136 SRs were not funded, accounting for 71.96%, and 53 SRs were funded, accounting for 28.04%. The most frequent source of financial assistance was from the National Natural Science Foundation of China for 11 SRs, accounting for 20.75% of all financial assistance. All details are shown in Table 1.

38 SRs were completed by three authors, accounting for 20.11%, followed by 2 and 4 authors, accounting for 16.93%, followed by 5 authors (25, 13.23%), 6 authors (18, 9.52%) and 7 authors (15, 7.94%). There were 15 (7.94%) SRs with 8 to 10 authors and 9 (4.76%) with 11 or more authors.

189 SRs were divided into four categories: conventional meta-analysis, network meta-analysis, narrative synthesis, and individual patient data (IPD) meta-analysis, with the number of 152 (80.42%), 21 (11.11%), 14 (7.41%), and 2 (1.06%). The types of research included in these SRs are diverse. The most included study type was RCTs, with 124 (65.61%) SRs. The other research types were relatively less included, including no restrictions (21, 11.11%), cohort studies (42, 22.22%), observational studies (26, 13.76%), case series (22, 11.64%), case report (14, 7.41%) and non-RCTs (12, 6.35%). All details are shown in Table 1.

Among the SRs included, March, April, May, and June were registered 25, 109, 50 and 5 SRs, respectively, accounting for 13.13%, 57.67%, 26.46% and 2.65% respectively. According to the specific date, the number of registered SRs on April 20, 2020 was the largest, with 14 SRs. The relationship between the specific date and the number of registered SRs is shown in Fig. 1.

Table 1
Basic information

Items	N	Percentage
Registration month		
March	25	13.23%
April	109	57.67%
May	50	26.46%
June	5	2.65%
Publication		
Review ongoing	178	94.18%
Review completed not published	11	5.82%
Report deviation risk assessment		
Yes	164	86.77%
No	25	13.23%
Bias risk assessment method		
Cochrane risk of bias	129	68.25%
NOS	44	23.28%
ROBINS	12	6.35%
Report analysis software		
Yes	100	52.91%
No	89	47.09%
Data analysis software		
Review Manager	60	31.75%
Stata	32	16.93%
R software	13	6.88%
SPSS	4	2.12%
Types of included studies		
No restrictions	21	11.11%
RCTs	124	65.61%
Cohort studies	42	22.22%

Items	N	Percentage
Observational studies	26	13.76%
Case reports	14	7.41%
Case series	22	11.64%
Cross-sectional studies	4	2.12%
Non-RCTs	12	6.35%
Funding		
None	136	71.96%
Yes	53	28.04%

3.2. Database

Of all the 189 SRs that met the standard, 188 searched the databases, only one did not. In the database of the report, 136 (72.34%) SRs were retrieved only in English database, and the remaining 52 (27.66%) searched both English and Chinese databases. Among the databases searched, PubMed/MEDLINE was the most frequently used database, followed by EMBASE (152, 80.85%), Cochrane Library (127, 67.54%), Web of Science (61, 32.45%), Scopus (37, 19.68%), and Google Scholar (34, 80.85%), The commonly searched Chinese databases were CNKI (49, 26.06%), Wangfang (35, 18.62%), and VIP (26, 13.83%). Commonly used database combinations were PubMed / MEDLINE and EMBASE (152, 80.85%), PubMed / MEDLINE combined with Cochrane Library (127, 67.55%), EMBASE and Cochrane Library (109, 57.98%), PubMed / MEDLINE, EMBASE, Cochrane Library and Web of Science (36, 19.15%). The detailed database retrieval is shown in Table 2.

Table 2
Report information of literature search

Category	Characteristic	N	%
Reported search strategy	Yes	188	99.47%
	No	1	0.53%
Language of databases searched	English	136	72.34%
	English-Chinese	52	27.66%
Name of database	WHO Trials	17	9.04%
	Web of Science	61	32.45%
	Wanfang	35	18.62%
	VIP	26	13.83%
	Scopus	37	19.68%
	PubMed/MEDLINE	187	99.47%
	MedRxiv/BioRxiv	16	8.51%
	Google Scholar	34	18.09%
	EMBASE	152	80.85%
	Cochrane Library	127	67.55%
	CNKI	49	26.06%
	ClinicalTrials.gov	26	13.83%
	CINAHL	21	11.17%
	CBM	29	15.43%
Combination of databases	PubMed/Medline + Embase + Cochrane Library	109	57.98%
	PubMed/Medline + Embase	152	80.85%
	PubMed/Medline + Cochrane Library	127	67.55%
	CNKI + PubMed/Medline	49	26.06%
	Embase + Cochrane Library	109	57.98%
	PubMed/Medline + Embase + Cochrane Library + Web of Science	36	19.15%

3.3. Country

A total of 39 countries participated in the SRs. 164 (86.77%)SRs were completed by one country, 18(9.52%) by two countries, 1(0.53%) by four countries and 1(0.53%)by six countries, and 1 by 18 countries. The largest number of registrations was in China(69, 36.50%), followed by the UK(22, 11.60%), Brazil(19, 10.05%), USA(13, 6.88%),Chile(9, 4.76%) and India(9, 4.76%). Canada (7, 3.70%), Iran(6, 3.17%)and Italy(6, 3.17%) also registered more than five SRs. There are 25 countries registered more than 1 SR, Table 3. The social network map of the cooperative relationship among the countries is drawn. And there are 27 cooperative relations formed among them, Fig. 2.

Table 3
Countries contributed to SRs in COVID-19 treatment (> 1) [N (%)]

Rank	Country	N(%)	Rank	Country	N(%)
1	China	69(36.50%)	14	Mexico	4(2.12%)
2	UK	22(11.60%)	15	Spain	4(2.12%)
3	Brazil	19(10.05%)	16	Australia	3(1.59%)
4	USA	13(6.88%)	17	Ethiopia	3(1.59%)
5	Chile	9(4.76%)	18	Israel	3(1.59%)
6	India	9(4.76%)	19	South Korea	3(1.59%)
7	Canada	7(3.70%)	20	Denmark	2(1.06%)
8	Iran	6(3.17%)	21	France	2(1.06%)
9	Italy	6(3.17%)	22	Germany	2(1.06%)
10	Egypt	5(2.64%)	23	Japan	2(1.06%)
11	Saudi Arabia	5(2.64%)	24	Peru	2(1.06%)
12	Colombia	4(2.12%)	25	Vietnam	2(1.06%)
13	Indonesia	4(2.12%)			

3.4. Institutions

A total of 301 institutions contributed to the registrations of COVID-19 SRs of treatment. 101 (53.44%) SRs were completed by one institution, 46 (24.34%) by two organizations, 23 (12.17%) by three organizations, 6 (3.17%) by four organizations, 5 (2.65%) by five organizations, 2 (1.06%) by six organizations, 2 (1.06%) by seven organizations, 2 (1.06%) by eight organizations, and 2 (1.06%) by 11 organizations.

The top four productive institutions are Chengdu University of traditional Chinese medicine (7, 3.70%), Liaoning university of traditional Chinese medicine (6, 3.17%), Children's hospital of Chongqing medical

University (4, 2.12%), King's college London (4, 2.12%), Table 4. A social network analysis of institutions revealed that 44 institutions formed a cooperative relationship, Fig. 3.

Table 4
Institutions contributed to SRs in COVID-19 treatment (> 2) [N (%)]

Rank	Institution	N(%)
1	Chengdu university of traditional Chinese medicine	7(3.70%)
2	Liaoning university of traditional Chinese medicine	6(3.17%)
3	Children's hospital of Chongqing medical university	4(2.12%)
4	King's college London	4(2.12%)
5	Affiliated hospital of Liaoning university of traditional Chinese medicine	3(1.59%)
6	All India institute of medical sciences	3(1.59%)
7	Cairo university	3(1.59%)
8	Fundación epistemonikos	3(1.59%)
9	King's college hospital	3(1.59%)
10	London north west university	3(1.59%)
11	McMaster university	3(1.59%)
12	Northwick park hospital	3(1.59%)
13	Royal free hospital	3(1.59%)
14	Tehran university of medical sciences	3(1.59%)
15	University college London	3(1.59%)
16	University of Toronto	3(1.59%)

3.5. Interventions

186 (98.41%) registrations reported interventions and 3(1.59%) did not. The reported interventions can be classified as antiviral therapy (81, 42.86%), respiratory support (16, 8.47%), circulation support (11, 5.82%), plasma therapy for convalescent patients (11, 5.82%), immunotherapy (9, 4.76%), TCM Treatment (9, 4.76%), rehabilitation treatment (5, 2.65%), anti-inflammatory treatment(16, 8.47%) and other treatments (31, 16.40%). In antiviral therapy (81, 42.86%), 11 (5.82%) registrations did not specify specific drugs, and 70 (37.04%) indicated the drugs to be used. The most commonly used drugs were chloroquine / hydroxychloroquine (26, 13.76%), followed by remdesivir (12, 6.35%), lobinavir / ritonavir (11, 5.82%), favipiravir (5, 2.65%), ribavirin (5, 2.65%), interferon (5, 2.65%), abiron (4, 2.12%), abidor (4, 2.12%), Table 5. The control measure was placebo or conventional medicine or no treatment (189, 100%).

Table 5
Interventions of SRs in COVID-19 treatment [N (%)]

Items	N	Percentage
Report		
Yes	186	98.41%
No	3	1.59%
Interventions		
Antiviral therapy	81	42.86%
Not reported	11	5.82%
Chloroquine / hydroxychloroquine	26	13.76%
Interferon	5	2.65%
Lobinavir / ritonavir	11	5.82%
Ribavirin	5	2.65%
Remdesivir	12	6.35%
Abiron	4	2.12%
Favipiravir	5	2.65%
Abidor	2	1.06%
Respiratory support	16	8.47%
Circulation support	11	5.82%
Plasma therapy for convalescent patients	11	5.82%
Immunotherapy	9	4.76%
TCM Treatment	9	4.76%
Rehabilitation treatment	5	2.65%
Anti-inflammatory treatment	16	8.47%
Other treatments	31	16.40%

3.6. Outcome measures

3.6.1. Primary outcome measures

Each SR included has multiple outcome indicators. The main outcome indicators are related to a series of symptoms, signs, examination, prognosis and so on. The most common outcome measure was mortality rate (92, 48.68%), followed by adverse events (28, 14.81%), time of becoming negative for the coronavirus

(22, 11.64%), survival rate (14, 7.41%), and length of hospital stay (14, 7.41%), time to achieve clinical recovery (13, 6.88%), defervescence time (13, 6.88%), effectiveness/effective rate (11, 5.82%). More main outcome measures are shown in Table 6.

Table 6
The top 20 primary outcome measures in terms of frequency [N (%)]

Rank	Primary outcome measures	N(%)	Rank	Primary outcome measures	N(%)
1	Mortality rate	92(48.68%)	11	Disease severity scores	9(4.76%)
2	Adverse events	28(14.81%)	12	Serum cytokine levels	8(4.23%)
3	Time of becoming negative for the coronavirus	22(11.64%)	13	Lung function	8(4.23%)
4	Survival rate	14(7.41%)	14	Length of stay in ICU	8(4.23%)
5	Length of hospital stay	14(7.41%)	15	Clinical signs	7(3.70%)
6	Time to achieve clinical recovery	13(6.88%)	16	Cure rate	6(3.17%)
7	Defervescence time	13(6.88%)	17	Time of disappearance of main symptoms	6(3.17%)
8	Effectiveness/Effective rate	11(5.82%)	18	Efficacy	6(3.17%)
9	Lung CT	9(4.76%)	19	Disease duration	5(2.65%)
10	Treatment safety	9(4.76%)	20	Duration of mechanical ventilation	5(2.65%)

3.6.2. Secondary outcome measures

In addition to the main outcome measures, 127 SRs also had secondary outcome indicators. The most commonly used secondary outcome measures were length of hospital stay (48, 25.40%), adverse events (43, 22.75%), ICU length of stay (30, 15.87%), mechanical ventilation (23, 12.17%), rate of viral nucleic acid turning negative (11, 5.82%), side effects (10, 5.29%). More details are shown in Table 7.

Table 7
The top 16 secondary outcome measures in terms of frequency [N (%)]

Rank	Secondary outcome measures	N(%)	Rank	Secondary outcome measures	N(%)
1	Length of hospital stay	48(25.40%)	9	Intubation rate	7(3.70%)
2	Adverse events	43(22.75%)	10	Time to clinical improvement	6(3.17%)
3	ICU length of stay	30(15.87%)	11	Tomography imaging	6(3.17%)
4	Mechanical ventilation	23(12.17%)	12	Levels of IL-6	5(2.65%)
5	Rate of viral nucleic acid turning negative	11(5.82%)	13	C-reactive protein	5(2.65%)
6	Side effects	10(5.29%)	14	Disease recovery	5(2.65%)
7	Acute respiratory distress syndrome	9(4.76%)	15	ALT	4(2.12%)
8	Adverse drug reactions	9(4.76%)	16	Renal replacement therapy	4(2.12%)

4. Discussion

The PROSPERO platform opened the COVID-19 retrieval channel, carried out reasonable and meticulous classification management of the literature, and the retrieved literature met the inclusion standards. By August 3, 2020, 122 of the 189 SRs included should have reached the expected completion time, but in fact, only 11 SRs were completed, with the completion rate of only 9.02%. It can be explained that the reasons for the low completion rate may be that the data resources obtained in the early stage are insufficient, the data acquisition method is difficult, the expected completion time is too short, and the difficulty of the research is estimated incorrectly. Therefore, in the future research, we should try our best to avoid it, and we should make a correct evaluation of the research, whether from the feasibility or the time. To achieve a reasonable planning progress, as far as possible in the scheduled time to complete.

Through the reports on the retrieval database, it is not difficult to see that among the 188 SRs, except for one which is a single database, the remaining 187 SRs are all joint retrieval of multiple databases to obtain the corresponding data. Among them, PubMed / MEDLINE combined with EMBASE (152, 80.85%) was used most. At the same time, 136 (72.34%) SRs retrieved only English databases, and the remaining 52 (27.66%) were combined with Chinese and English databases. In this view, most of the databases are limited to English, and their data are not representative enough to a certain extent. The above shows that in the use of databases, it is advisable to search multi language databases at the same time to make the data more representative.

164 (86.77%) SRs were completed by one country independently, and 25 (13.23%) SRs were completed by cooperation. 69 (36.51%) of the SRs were undertaken by China, 22 (11.64%) by UK and 19 (10.05%) by Brazil. A total of 39 countries have participated in the registered SRs and 27 (69.23%) countries have formed cooperative relations. UK has the largest cooperation intensity, followed by China, Canada, Egypt, and Italy. A total of 301 institutions contributed to the registered SRs and 232 (77.08%) had cooperative relations. Chengdu University of traditional Chinese medicine has undertaken 7 (3.7%) projects, Liaoning University of traditional Chinese medicine has undertaken 6 (3.17%) projects, and children's Hospital of Chongqing Medical University has undertaken 4 (2.12%) projects, all of which are located in China. In the future, researchers should strengthen more comprehensive research and carry out extensive cooperation between countries and institutions.

3 (1.59%) of the included SRs did not report intervention methods. According to the treatment methods of China's COVID-19 diagnosis and treatment plan (Six Edition), the interventions in the rest of the literatures (186, 98.41%) were manually divided into the following categories: antiviral therapy (81, 42.86%), respiratory support (16, 8.47%), circulation support (11, 5.82%), plasma therapy for consistent patients (11, 5.82%), immunotherapy (9, 4.76%), TCM treatment (9, 4.76%), rehabilitation treatment (5, 2.65%), anti-inflammatory treatment (16, 8.47%) and other treatments (31, 16.40%). We focused on antiviral treatment (81, 42.86%), of which 11 SRs did not specify the specific drugs. The most common used drugs were chloroquine / hydroquinone (26, 13.76%), followed by remdesivir (12, 6.35%), lobinavir / ritonavir (11, 5.82%), favipiravir (5, 2.65%), ribavirin (5, 2.65%), interference (5, 2.65%), abiron (4, 2.12%), abidor (4, 2.12%). This shows that there are a lot of repeated studies and there may be a waste of scientific research resources. The description of intervention measures was not standard enough. The included literature did not describe the treatment method, dosage and time in detail. Therefore, in the future research, researchers should be more careful to check the registered projects to avoid repeated research. Interventions used should be described in more detail and in a more standardized way.

Among all the outcome indicators, the most important outcome indicators were mortality rate (92, 48.66%), then adverse events (28, 14.81%) and the time of becoming negative for the coronavirus (22, 11.64%); the most frequently used secondary outcome was length of hospital stay (48, 25.40%), and then adverse events (43, 22.75%), ICU length of stay (30, 15.87%) and mechanical cultivation (23, 12.17%). By comparing the two types of outcome indicators, the common items were length of hospital stay, adverse events, ICU length of stay, the time of becoming negative for the coronavirus, and monitoring of mechanical ventilation. However, there are some differences between the two. The main outcome indicators are monitoring clinical symptoms and signs, while the secondary outcome indicators tend to be prognostic indicators, laboratory test data (IL-6, C-reactive protein, ALT), and the adverse reactions mainly focus on adverse drug reactions. Therefore, we can see that the determination of outcome indicators should be complementary as far as possible, so as to obtain more detailed and perfect information of outcome indicators, and avoid excessive repetition.

5. Conclusions

Many COVID-19 SRs of treatment have been registered, but the completion rate was low. China was the country with the largest number of registrations, Chengdu University of traditional Chinese medicine was the institution with the largest output. The cooperation between countries is not close enough, and the cooperation between institutions is relatively close. More comprehensive and extensive collaborations between different institutions and different regions should be further strengthened to strengthen communication, share information, and obtain more representative experimental results. More repetitive research will lead to a waste of scientific research resources. More attention should be paid to the access to the registration, so as to avoid duplicate research. More attention should be paid to the deficiency of interventions and outcome measures, and the standardization of results should be strengthened.

Abbreviations

COVID-19

Corona virus disease 2019; Treatment:Traditional Chinese Medicine; SARS-CoV-2:Severe acute respiratory syndrome coronavirus 2; SR:Systematic review.

Declarations

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Author contributions

RNZ, YG and JHT planned and designed the study. RNZ, YG, RNL and DRX participated in the literature search and data collection. RNZ, YG, and JHZ analyzed the data. RNZ and YG drafted the manuscript. RNZ, YG, DRX and JHT revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data will be made available upon request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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Figures

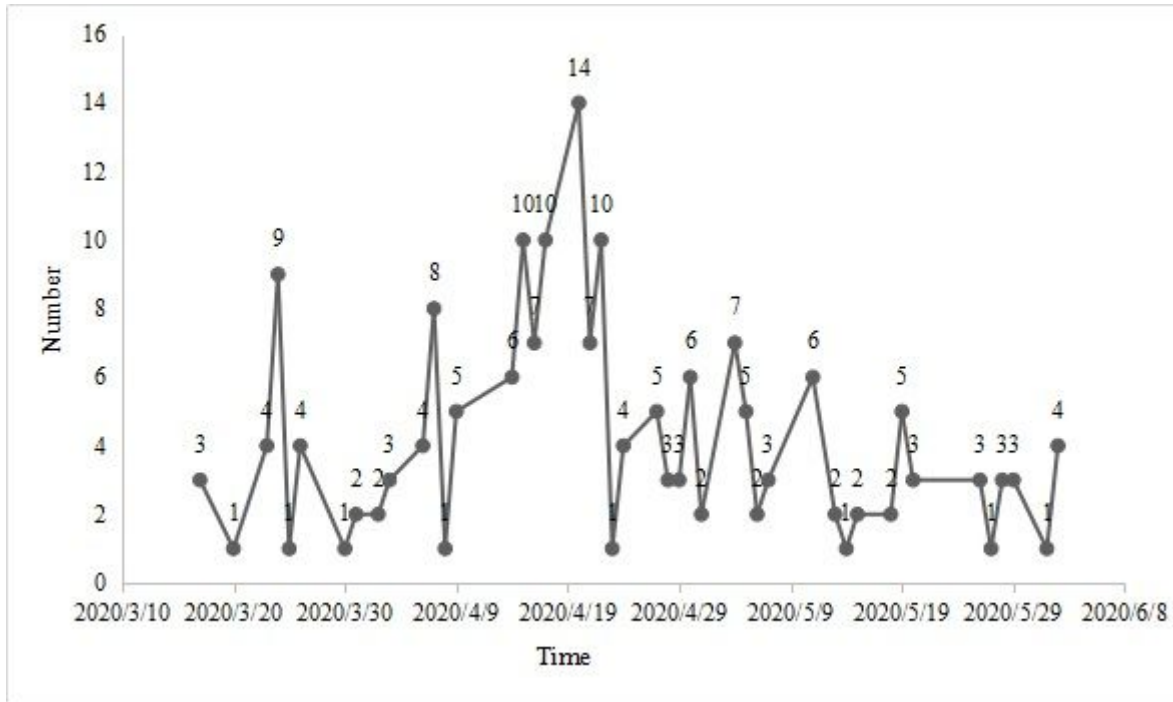


Figure 1

Registration Time of COVID-19 Related to Treatment

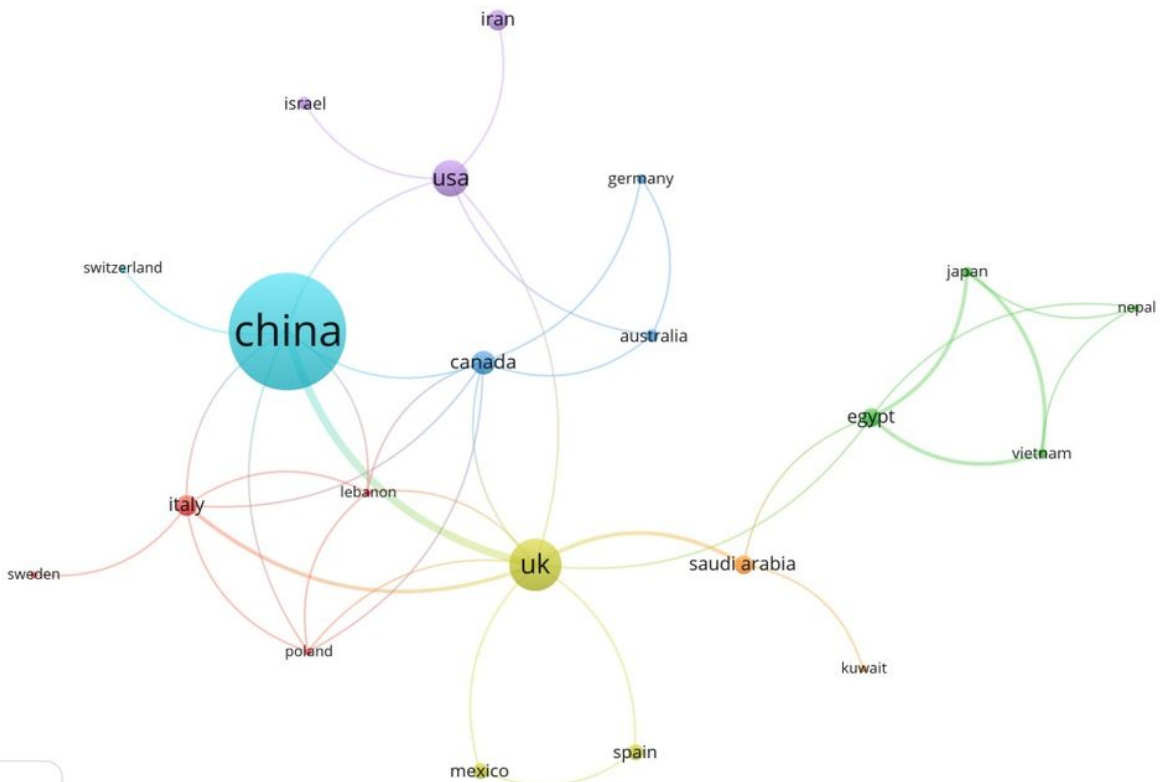


Figure 2

A social network analysis of countries

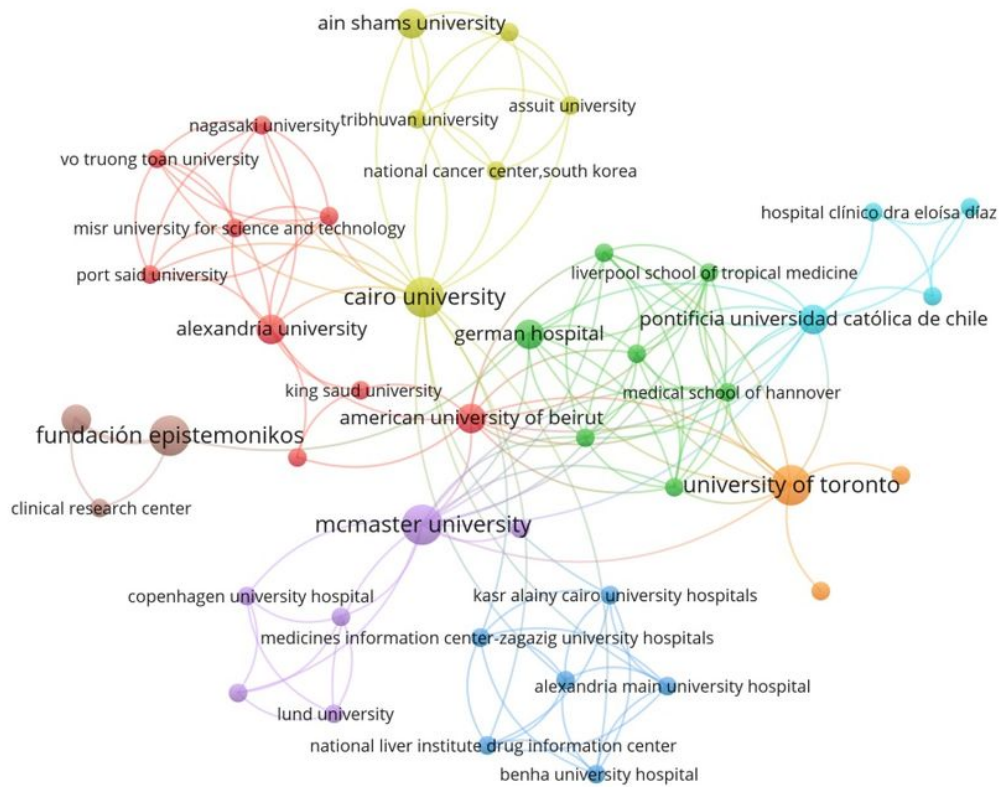


Figure 3

A social network analysis of institutions