

Focusing on the Treatment of COVID-19: A Comprehensive Analysis of 226 Trials Registered on Clinicaltrials.gov and ChiCTR

Jincai Guo

Changsha Stomatological Hospital

Hui Xie (✉ kqyyxh1@126.com)

Changsha Stomatological Hospital <https://orcid.org/0000-0002-4216-2660>

Hao Wu

Changsha Stomatological Hospital

Research

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Abstract

Background: The purpose of this study is to analyze the registered clinical trials of COVID-19, and to provide a reference for the clinical treatment of COVID-19.

Methods: Chinese Clinical Trial Registry (ChiCTR) and Clinicaltrials.gov databases were searched for clinical trials of COVID-19, which were registered from inception to February 29, 2020, to screen out the clinical trials on the treatment of COVID-19, and the research units and regions, sample size, study types, study stages, and intervention measures were analyzed.

Results: There were 226 clinical trials on COVID-19 in the 2 databases, and all of them were registered by research units in China. The top five registered areas were Hubei, Beijing, Shanghai, Guangdong, and Zhejiang. The study type was as follows: interventional study (207, 91.6%) and observational study (18, 8.0%). Clinical trial staging was as follows: exploratory studies/preliminary trials (91, 40.3%), phase I trials (4, 1.8%), phase II trials (12, 5.3%), phase III trials (12, 5.3%), phase IV trials (47, 20.8%), phase I/II trials (2, 0.9%), phase II/III trials (5, 2.2%), and other trials (57, 25.2%). Intervention measures were as follows: there were 143 (63.3%) trials of western medicine treatment, 50 (22.1%) trials of Chinese medicine treatment, and 21 (9.3%) trials of integrated Chinese medicine treatment and western medicine treatment.

Conclusion: Researchers have registered a large number of clinical trials in a short time. The number of existing patients of COVID-19 is not enough to support hundreds of clinical trials. There is a lack of multicenter, randomized, double-blind, placebo-controlled trials.

Background

The Coronavirus Disease 2019 (COVID-19) was first detected in Wuhan, China in December 2019; it quickly attracted worldwide attention¹ and rapidly spread to most provinces in China and many countries; thus, showing an outbreak trend. The most common symptoms of COVID-19 were fever and cough^{2,3}. Since January 23, 2020, China has launched a level-1 response to major public health emergencies in many provinces and cities, which has subsequently been designated as a public health emergency of international concern by the World Health Organization. According to data from the official website of the National Health Commission of China, as of March 20, 2020, a total of 81,008 COVID-19 cases were confirmed in China, with 3,255 deaths. As of July 31, 2020, there have been a total of 89,374 confirmed cases in China, including 4,666 deaths; a total of 17,106,007 cases and 668,910 deaths have been confirmed around the globe, including 4,388,566 in the United States of America, 2,552,265 in Brazil, and 839,981 in Russian Federation, which was reported on the official website of the WHO. At present, there is no specific treatment for COVID-19.

The outbreak of COVID-19 poses a great challenge to epidemic prevention and control. At present, there is no vaccine for COVID-19; thus, identifying drug treatment options as soon as possible is critical for the response to COVID-19. Researchers are endeavoring to discover drugs for the treatment of COVID-19. Sheahan et al.⁴ reported that Remdesivir is a potential drug for treating coronavirus. The first patient in the United States received Remdesivir treatment, and fever subsided the next day, with significant relief of breathing difficulties⁵. Colson et al.⁶ reported that Hydroxychloroquine and Chloroquine would be a good choice for the treatment of COVID-19. Wang et al.⁷ found that Remdesivir and chloroquine effectively inhibit COVID-19 *in vitro*. Chen et al.⁸ commented that convalescent plasma is a potential therapy for COVID-19. Clinical application showed that some traditional

Chinese medicine treatments for COVID-19 have a good effect⁹. However, the efficacy and safety of these drugs for treating COVID-19 still need to be further confirmed by clinical experiments. Therefore, many clinical researchers have registered a large number of clinical trials in Clinicaltrials.gov and Chinese Clinical Trial Registry (ChiCTR), with an aim to explore effective treatment measures for COVID-19 through clinical trials. Clinicaltrials.gov was jointly developed in 1997 by the U.S. National Institutes of Health and the U.S. National Library of Medicine, together with the U.S. Food and Drug Administration, and it started operating in 2000. It is a clinical trial registration website with the largest number of registrations and the widest coverage of countries in the world¹⁰. The Chinese Clinical Trial Registry (ChiCTR) is a primary Registry of the World Health Organization International Clinical Trial Registration Platform (WHO ICTRP), which accepts clinical trial registration performed in China and around the world¹¹. There are many clinical trials on the treatment of Coronavirus Disease 2019 (COVID-19); however, there is a lack of systematic understanding of the clinical trials of COVID-19. In this study, we aimed to analyze the characteristics of registered clinical trials for the treatment of COVID-19. Clinical trials registered in the Clinicaltrials.gov and ChiCTR databases were comprehensively retrieved, and the trials for treatment of COVID-19 were selected and the registration contents were analyzed and summarized, as reported in the following sections.

Methods

1.1 Inclusion and exclusion criteria

1.1.1 Inclusion criteria

Clinical trials for the treatment of COVID-19 that were successfully registered in ChiCTR and Clinicaltrials.gov from inception to February 29, 2020.

1.1.2 Exclusion criteria

Exclusion criteria consisted of: clinical trials whose registration had not been completed as of February 29, 2020; incomplete clinical trials registry; and clinical trials for non-treatment of COVID-19, such as prevention studies, diagnostic studies, and epidemiological studies.

1.2 Retrieval strategy

A comprehensive search of ChiCTR and Clinicaltrials.gov was performed for clinical trials on the treatment of COVID-19. The ChiCTR database was searched using the registration title "新型冠状病毒 or 新冠 or COVID-19" as the project screening criteria. In the Clinicaltrials.gov database, "COVID-19 or 2019-nov or novel coronavirus" was entered in the condition or disease search box to retrieve the information.

1.3 Literature selection and data extraction

According to the inclusion and exclusion criteria, two reviewers independently screened trials, extracted contents, and checked with each other. If there was a difference in opinion among them, a third reviewer helped to judge, discuss, and make a decision. If contents were not complete, an attempt was made to contact the registrar to complete the contents. When screening the contents of trials, the title was first assessed and studies that did not meet the inclusion criteria were excluded. Then the contents of the registered trials were carefully read, and it was decided whether the trials should be included based on the inclusion and exclusion criteria. The extracted

contents were as follows: registration number, registered title, registered unit, area, whether or ethical approval was obtained, funding, research type, research phase, research design, interventional measure, sample size, masking, research place, and research time. All of the contents mentioned above were placed into an Excel sheet.

1.4 Statistical analysis

Excel (2010 version) was used for statistical analysis, and frequency and composition ratio were mainly used for descriptive statistical analysis.

Results

2.1 Results of registration and inclusion

On January 23, 2020, the first clinical trial of COVID-19 was registered by Wuhan Jinyingtan Hospital. As of February 29, 2020, 311 clinical studies of COVID-19 were registered in 38 days, with an average of 8 trials registered every day. Among them, 246 trials were registered in ChiCTR and 65 trials were registered in Clinicaltrials.gov. According to the strict inclusion and exclusion criteria, the title and registered content were carefully read and 85 clinical trials were excluded, including 24 diagnosis trials, 21 non-COVID-19 patient trials, 20 clinical characteristics trials, 13 epidemiological trials, 9 prevention trials, 4 incomplete registration information trials, 3 prediction model trials, and 1 animal experiment. After excluding studies that did not meet the inclusion criteria, 226 trials were included, including 178 trials in the ChiCTR database and 48 trials in the Clinicaltrials.gov database.

2.2 Basic characteristics of the included trials.

All of the 226 included trials were registered by Chinese research institutes. The top five locations of research institutes were Hubei (49, 21.7%), Beijing (28, 12.4%), Shanghai (28, 12.4%), Guangdong (25, 11.1%), and Zhejiang (23, 10.2%). A total of 89 (39.4%) trials were conducted in Hubei Province, China, including 9 in Beijing, 12 in Shanghai, and 5 in Guangdong. Among the 226 included trials, 82 (36.3%) trials were funded by government departments, 44 (19.5%) trials were funded by hospitals, 14 (6.2%) trials were funded by universities, 21 (9.3%) trials were funded by medical companies, and 62 (27.4%) trials were self-financed. A total of 91 (40.3%) trials were exploratory studies/preliminary experiments, 4 (1.8%) clinical trials were phase I, 12 (5.3%) clinical trials were phase II, 12 (5.3%) clinical trials were phase III, 47 (20.8%) clinical trials were phase IV, 2 (0.9%) clinical trials were phase I/II, 5 (2.2%) clinical trials were phase II/III, and 57 (25.2%) clinical trials were not applicable to phase. The status of the included trials was as follows: recruiting (120, 53.1%), not yet recruiting (102, 45.1%), suspended (3, 1.3%), and enrolling by invitation (1, 0.4%). All of the basic characteristics of the included trials are shown in Table 1.

2.3 Characteristics of the study design

The total sample size of 226 included trials was 32,815, with an average sample size of about 145. There were 53 (23.5%) trials with a sample size of less than 50 and 54 (23.9%) studies with a sample size of 50–99. There were 111 (49.1%) studies with a sample size of 100–499, 7 (3.1%) studies with a sample size of 500–1000, and 1 (0.4%) study with a sample size of more than 1000. Of the 226 trials, 69 (30.5%) trials were scheduled to be completed in 0–3 months, 55 (24.3%) trials were scheduled to be completed within 4–6 months, 73 (32.3%) trials were scheduled to be completed within 6–12 months, 19 (8.4%) trials were scheduled to be completed over 12

months, and 10 (4.4%) trials did not indicate the study time. The types of trials were as follows: interventional studies (207, 91.6%), observational studies (18, 8.0%), and another type of study (1, 0.4%). Most methods of study design were randomized parallel control (158, 69.9%). Besides, there were non-randomized parallel control (25, 11.1%), single-arm (20, 8.8%), prospective cohort studies (3, 1.3%), retrospective cohort (3, 1.3%), consecutive cohort studies (13, 5.7%), and factorial analysis (4, 1.8%). Among the 226 included trials, 38 (16.8%) trials were designed as the blind method, 116 (51.3%) trials were designed as an open-label study, and 72 (31.9%) trials did not state whether blinding was performed. There were 161 (71.2%) single-center studies and 65 (28.8%) multi-center studies. All of the characteristics of the study design are shown in Table 2.

2.4 Interventional methods of the included trials

According to the treatment performed in the 226 included trials, there were 143 (63.3%) western medicine treatments, 50 (22.1%) traditional Chinese medicine treatments, 21 (9.3%) integrated traditional Chinese medicine and western medicine treatments, and 12 (5.3%) other interventional methods. The main types of western drugs for COVID-19 included anti-viral, anti-dysenteric, immunomodulators, cell-based therapies, corticosteroids, monoclonal antibody, inhalation therapy, nutrition, and non-drug treatment. Western medicine mainly focused on Mesenchymal stem cell (14), Hydroxychloroquine (10), Lopinavir/Ritonavir (8), Abidor (7), Chloroquine (7), Convalescent plasma (6), Methylprednisolone (6), Favipiravir (5), and Remdesivir (3). There are also some combinations of drugs to treat COVID-19, such as Lopinavir/Ritonavir+Ribavirin+Interferon β 1b, and Darunavir+Cobicistat. All of the interventional methods of western medicine are shown in Table 3. There were 50 traditional Chinese medicine treatments, such as Xiyanping injection (3), Honeysuckle (2), and Shuanghuanglian oral liquid (1). Besides, there were several very interesting traditional Chinese medicine studies, such as shadowboxing, qigong practice, acupuncture, and Chinese massage.

Discussion

This study was a descriptive evaluation of clinical trials for the treatment of COVID-19, which were registered in Clinicaltrials.gov and ChiCTR. Since the outbreak first occurred in China, all of the clinical trials for the treatment of COVID 19 were registered by Chinese investigators.

The study found that a large number of clinical trials (246) for COVID-19 were registered in a short time (38 days). However, an additional 249 clinical trials were registered in Clinicaltrials.gov and ChiCTR, while we were writing this article from March 1, 2020 to March 21, 2020. This is an unprecedented number of trials for a disease in a short time. This indicates that many clinical researchers are trying to identify a safe and effective treatment for COVID-19 during the outbreak of the epidemic.

Besides, it also shows that clinical researchers in China pay more attention to the registration of clinical trials, which is also related to the submission requirement of many well-known journals at home and abroad stating that clinical trials must be registered before publication¹²⁻¹⁴. The locations of research units were mainly in Hubei Province, China because Hubei Province, especially Wuhan, was the hardest-hit area of the epidemic. Besides, many trials were registered in Beijing, Shanghai, Guangdong, Zhejiang, and Sichuan Provinces. These provinces are economically advanced, and they invested a lot in medical research. A large proportion of trials in these provinces was registered by medical staff who assisted Hubei in fighting the epidemic, and the trials were conducted in Hubei. Among the 226 included trials, 142 (62.8%) trials were funded by government departments, hospitals, and universities. This shows that the Chinese government attaches great importance to the prevention

and control of the epidemic and has rapidly invested a large number of research funds¹⁵. Only 21 (9.3%) trials were funded by medical companies, and this can reduce potential publication bias due to corporate sponsorship. However, 62 (27.4%) trials were self-financed. Clinical research requires a great deal of manpower and resources, which may be interrupted by a lack of funds.

The planned study time of the 226 included trials is mainly 1–6 months, which is mainly related to the urgency and timeliness of the COVID-19 epidemic. Most of the registered trials were large sample-sized studies, with an average sample size of 145 and a total sample size of 32,815 for 226 included trials. By March 20, 2020, China had a total of 81,008 confirmed cases, most of which have been cured and discharged from the hospital. Currently, only 6,314 cases have been confirmed in the hospital. However, an additional 249 clinical trials were registered in Clinicaltrials.gov and ChiCTR from March 1, 2020 to March 21, 2020. New trials are still being registered, and the number of existing patients of COVID-19 is not enough to support hundreds of clinical trials¹⁶. This is an important thing that researchers must consider. There have been 3 cancellations of registration applications due to the insufficient number of patients. With the basic control of the epidemic in China, those who are planning to apply or have applied for trials or are preparing to carry out trials must investigate whether the recruitment of researchers can be completed to avoid the waste of research resources. Clinical trials of COVID-19 may need to be carried out in badly infected countries outside China, such as Italy, Iran, and Spain.

The treatment of COVID-19 mainly focused on anti-viral, anti-dysenteric, immunomodulators, cell-based therapy, corticosteroids, monoclonal antibody, and traditional Chinese medicine. Among them, the potential drugs to treat COVID-19 were Mesenchymal stem cell, Hydroxychloroquine, Lopinavir/Ritonavir, Methylprednisolone, Abidor, Chloroquine, Convalescent plasma, Favipiravir, and Remdesivir. Based on a retrospective cohort study of 201 patients, Methylprednisolone therapy may be beneficial for COVID-19 patients who develop acute respiratory distress syndrome¹⁷. It has been found in the clinical application that numerous traditional Chinese medicines have a good effect on COVID-19. Scholars have adopted western medicine to conduct clinical trials of many traditional Chinese medicine treatments for COVID-19, which will provide scientific experimental evidence for traditional Chinese medicine treatment of COVID-19 and will be accepted by more people. Through a systematic analysis of the existing data, Chen et al. found that traditional Chinese medicine could be used as adjuvant therapy for the treatment of COVID-19¹⁸. Although the preliminary results of some clinical trials have found that the above drugs have a therapeutic effect on COVID-19, we will not know whether they are safe and effective in the treatment of COVID-19 until the clinical trials are completed. The experimental stages were mainly exploratory research/pre-experimental stage and phase 4 trials, among which 91 trials were exploratory research/pre-experimental stage and 47 trials were phase 4 trials. COVID-19 is a new disease; thus, there are many exploratory/pre-experimental studies, most of which are traditional Chinese medicine, integrated traditional Chinese medicine, and western medicine treatment. Phase 4 trials mainly involve the new use of some old drugs, such as Chloroquine, Hydroxychloroquine, Abilol, and Methylamrydrine, which are clinically proven safe drugs. Some drugs are effective against viral diseases.

Of the 226 clinical trials, 158 were randomized parallel assignment and only 38 were blind in their design. Most of the trials were not blind in their design. In this way, the results are prone to selective bias; thus, affecting the quality and credibility of the trials. If there is no high-quality research carried out by the design, then it is impossible to provide high-quality clinical research. The results of clinical trials will be questioned. This will also cause a serious waste of research resources.

Some questions have to be considered to use clinical trials to guide the epidemic prevention of COVID-19. First, to avoid wasting resources, researchers should try to conduct multicenter, randomized, double-blind, placebo-controlled trials, to reduce the number of low-quality clinical trials. Second, researchers must conduct clinical trials in strict accordance with the design, or their effort will not yield qualified results. Third, most of the researchers were medical workers on the front line of COVID 19 treatment, and they did not have enough time to complete clinical trials due to the heavy workload caused by the severe epidemic. It may be a good choice to involve professional research teams to assist them in completing the clinical trials. Fourth, a platform is needed to share and analyze the results of clinical studies so that doctors can get the information immediately and apply the results to the treatment of COVID 19 patients. Fifth, instead of waiting for a paper to be published, researchers should share the results of clinical trials in a timely manner. Sixth, it is necessary to establish a unified standard to evaluate the effect of COVID-19 treatment, to compare the effect of different treatment regimens, and explore to a better treatment method.

There are some limitations to this study. This study only analyzed the registered trials in the two databases as of February 29, 2020. After February 29, 2020, many trials were registered, in the process of registration, or had not started registration. Thus, this study could not fully reflect all of the clinical trials of COVID-19. However, this paper analyzed more than 300 registered trials, and the large number was representative to some extent, which could reflect the current clinical trial registration of COVID-19. In addition, some clinical trial registries were incomplete and researchers could not be contacted to supplement the registries, which may lead to biased results.

Conclusion

This study analyzed the registry of clinical trials for the treatment of COVID. Researchers have registered a large number of clinical trials in a short time. There are some potential drugs for COVID-19. With China's success in fighting the COVID-19 epidemic, the number of existing patients of COVID-19 is not enough to support hundreds of clinical trials. Some trials may not have been completed. There is lack of design of multicenter, randomized, double-blind, placebo-controlled trials. Doctors should pay close attention to the results of high-quality clinical trials, and they should translate good results in clinical practice in a timely manner for the treatment of COVID-19.

Abbreviations

COVID-19: Corona Virus Disease 2019;

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

JG and HW screened the literature and extracted and analyzed the data. JG proposed the preliminary concept of the study and drafted the article. HX read and approved the final manuscript.

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Tables

Table 1 Basic characteristics of the included trials

Characteristics	Number	Percentage (%)
Location		
Hubei	49(49)	21.7
Beijing	28(9)	12.4
Shanghai	28(12)	12.4
Guangdong	25(5)	11.1
Zhejiang	23(0)	10.2
Sichuan	10(3)	4.4
Chongqing	7(0)	3.1
Henan	7(0)	3.1
Jiangxi	7(1)	3.1
Tianjin	6(3)	3.1
Shanxi	6(2)	2.7
Jiangsu	6(0)	2.7
Other ¹	24(5)	10.6
Sponsor		
Government	82	36.3
Hospital	44	19.5
University	14	6.2
Company	21	9.3
Self-financing	62	27.4
Not stated	3	1.3
Stage		
0	91	40.3
I	4	1.8
II	12	5.3
III	12	5.3
IV	47	20.8
I/II	2	0.9
II/III	5	2.2
Other	57	25.2

Status			
Recruiting	120	53.1	
Not yet recruiting	102	45.1	
Enrolling by invitation	1	0.4	
Suspending	3	1.3	

Other: Hunan4(0), Anhui4(0), Fujian3(2), Heilongjiang3(0), Shanxi2(1), Jilin2(1), Shandong2(0), Guizhou1(0), Liaoning1(0), Neimengu1(1), Hongkong1(0)

Table 2 Study design elements of trials

Types	Number	Percentage (%)
Sample Size		
1-49	53	23.5
50-99	54	23.9
100-499	111	49.1
500-999	7	3.1
³1000	1	0.4
Average	145	
Amount	32815	
execute time		
0-3 months	69	30.5
4-6 months	55	24.3
6-12 months	73	32.3
over 12 months	19	8.4
Not stated	10	4.4
Study type		
Interventional	207	91.6
Observational	18	8
other	1	0.4
Intervention model		
randomised parallel control	158	69.9
non-randomized parallel control	25	11.1
single-arm	20	8.8
prospective cohort	3	1.3
retrospective cohort	3	1.3
consecutive cohort	13	5.7
factorial analysis	4	1.8
Masking		
blind	38	16.8
Open Label	116	51.3
Not stated	72	31.9
Center		

single-center	116	71.2
multi-center	65	28.8

Table 3 Overview of the western medicine treatment for COVID-19

Types	Name and number of treatment
Anti-viral	Lopinavir/Ritonavir (8), Abidor (7), Favipiravir (5), Ridsivir (3), ASC09 (1), ASC09/ritonavir (2), Azvudine (2), Triazaverine (1), Baloxavir (1), Marboxil (2), Danoprevir+ritonavir (3), Darunavir+Cobicistat (1), Danovir+Ritonavir (1), Favipiravir+ Interferon a (1), Danoprevir+ Lopinavir/Ritonavir (1), ASC09F+Oseltamivir/Ritonavir+Oseltamivir(1),Ribavirin+Lopinavir/Ritonavir+Interferon a-1b(1), Lopinavir/Ritonavir+Ribavirin+Interferon β1b (1)
Anti-dysenteric	Hydroxychloroquine (10), Chloroquine (7), Dihydroartemisinin piperazine (1)
Immunomodulators	Immunoglobulin (2), Thalidomide (2), Polyinosinic-polycytidylic Acid (1), Fluorine (1), Thymosin (1), Fingolimod (1)
Cell-based therapy	Mesenchymal stem cell (14), Convalescent plasma (5), NK Cells (2), Pathogen-specific DC and CTLs (1), Palace blood stem cell (1), Immune serum (1), Cord blood CIK+NK cells (1), Cord blood mononuclear cells (2), Cord blood plasma (1), Recombinant human colony-stimulating factor (1), Recombinant human interferon a1b (1), Recombinant interferon α1β (1), Recombinant viral macrophage inflammatory proteins (1), Recombinant Human Angiotensin-converting Enzyme 2 (1), interferon α+Antiviral drugs +Recombinant Human Trefoil Factor-2 (1)
Corticosteroids	Methylprednisolone (6)
Monoclonal antibody	Tocilizumab (2), Bevacizumab (1), Adalimumab (1), Carrilizumab (1), PD-1 (2), Anti-CD147 (1)
Inhalation therapy	Oxyhydrogen (1), Nitric Oxide (1), Ozone autohemotherapy (1), Hydrogen (1)
Nutrition	Vitamin C (3), Vitamin D (1), Thiocetic Acid (1), Microecologics (3), Nutrition Support (2), Vitamin C + Diammonium Glycyrrhizinate (1),
Other drugs	Ruxolitinib (1), Pirfenidone (1), Jakotini (1), Aescinate (1), Tranilast (1), Dipyridamole (1), SuraminSodium (1), Carrimycin (1), ACEI (1), GD31 (1), T89 (1), Human placental biologics (1)
Non-drug treatment	Pulmonary Rehabilitation (3), ECMO (2), Ultrashort wave (1), Walking training (1), Regulation of body and mind (1), Humanistic care (1), Mobile Health training (1), Renal replacement therapy (1), Simplify cognitive behavior therapy (1)