Research Square

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A Survey of Characteristics and Potential Contribution of Registered Studies for 2019 novel coronavirus disease (COVID-19)

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Abstract

Background

The World Health Organization characterized the 2019 novel coronavirus disease (COVID-19) as a pandemic on March 11. Many clinical trials on COVID-19 have been registered, and we aim to review the characteristics of the trials and provide guidance for future trials to avoid duplicated effort.

Methods

All the studies on COVID-19 registered before Mar 3, 2020 on eight registry platforms worldwide were searched and the data of design, participants, interventions, and outcomes were extracted and analyzed. The most promising trials were screened based on study design, rationale, and resource availability.

Results

393 studies registered were identified until Mar 3 2020 and 380 (96.7%) studies were from mainland China, while 3 in Japan, 3 in France, 2 in the US, and 3 were international collaborative studies. 363 studies (92.4%) recruited participants from hospitals and 266 studies (67.7%) aimed at therapeutic effect, others were for prevention, diagnosis, prognosis, etc. 202 studies (51.4%) were randomized controlled trials (RCTs). The average sample size was 1061 and ranged from 8 to 150,000 per study. 177 out of 266 therapeutic studies (66.5%) tested Western medicines including antiviral drugs (17.7%), stem cell and cord blood therapy (10.2%), chloroquine and derivatives (8.3%), 16 (6.0%) on Chinese medicines, and 73 (27.4%) on integrated therapy of Western and Chinese medicines. 14 Chinese medicines had its clear rationale for evaluation of therapeutic effects. 31 studies among 266 therapeutic studies (11.7%) used mortality as primary outcome, while the most designed secondary outcomes were symptoms and signs (47.0%). 106 studies (27.0%) were funded by the government, and 268 (68.2%) demonstrated ethical approval. 45.5% studies (179 out of 266) had not started recruiting till Mar 3. Eight RCTs were evaluated as the most promising trials.

Conclusions

Majority of the studies focused on assessing therapeutics for COVID-19 but inappropriate outcome setting, delayed recruitment and insufficient numbers of new cases in China implied many studies may fail to complete. Strategies and protocols of the studies with robust and rapid data sharing from international collaboration are warranted for emergency public health events, helping to accelerate priority setting for timely evidence-based decision-making.

Background

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [1]. 2019 novel coronavirus disease (COVID-19) occurred in December 2019 and the first case was reported in Wuhan, China [2]. On January 31, 2020, the World Health Organization (WHO) announced that the new coronavirus epidemic constituted a public health emergency of international concern and characterized COVID-19 as a pandemic on March 11[3]. As of April 22, 2,565,879 people were confirmed infected with COVID-19 worldwide in 210 countries, areas or territories with cases [4]. While carrying out public health control and clinical management, Chinese government also encouraged speeding up clinical trials of new drugs, and it was necessary to promptly launch them into the frontline of treatment, improve cure and reduce death [5]. As there is no specific treatment for COVID-19, and the main management is for symptomatic treatment and supportive care, clinical evidence is urgently needed to support clinical decision-making. Researchers in China reacted quickly, and the first clinical trial was registered in the China clinical trials registry on Jan 23 2020. Following a short period, more than 200 clinical trials have been registered, involving a variety of therapeutic approaches [6]. Facing the increasing ongoing trials, it would be important to review the research questions and characteristics of these studies to inform clinical practice for the prevention and treatment of COVID-19. These questions need to be answered for our increased understanding of the most promising trials.

Therefore, our aim is to investigate the current status and characteristics of the registered studies, providing guidance for future trials and avoiding duplicated effort worldwide.

Methods

Search strategy

All the clinical studies on COVID-19 registered before Mar 3 2020 on the trial registry platforms were retrieved, including the United States ClinicalTrials.gov (http://clinicalTrials.gov), Chinese clinical trial registry (ChiCTR) (http://www.chictr.org.cn), Acupuncture-Moxibustion Clinical Trial Registry (http://www.acmctr.org/index.aspx), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au), Japan Primary Registries Network (https://jrct.niph.go.jp), the United Kingdoms' ISRCTN registry (http://www.isrctn.com), Clinical Trials Registry-India (http://ctri.nic.in) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). The search terms included COVID-19, Corona Virus Disease 2019, novel coronavirus, 2019-nCoV, and SARS-CoV-2.

Data extraction

Nine authors (MX, YJ, YZ, YYZ, YXS, ZYT, XYJ, QBJ, MY) abstracted data extraction in parallel, including registration number and date, title, e-mail, leading institutions, country and province, setting, ethic information, funding, design, study objectives, anticipated start date, interventions and control, population, sample size, recruiting status and outcomes. We also checked the numbers of confirmed cases in China from the official website of the National Health Commission of the People's Republic of China [7]. All abstracted data were entered into a pre-defined data extraction sheet.

Screen for promising trials

We designed the criteria for the most promising trials as follow:

- Those with a rigorous design (randomized controlled trials, RCTs) for therapeutic effects;
- Those testing a treatment with a good rationale for safety and effectiveness, with existing evidence of human studies on COVID-19, pneumonia, SARS, Ebola, MERS, influenza, human immunodeficiency virus (HIV) and other viral diseases;
- Treatments which are widely available (e.g. Chinese herbal medicines);
- Those measuring important outcomes (mortality or exacerbation as primary outcomes);
- Those with a reasonable sample size (estimated based on hypothesis, and a reasonable chance of completing recruitment).

The trials were screened with the data extraction sheet, and the supporting evidence was searched on PubMed, characteristics of the eligible RCTs were extracted.

Statistical analysis

The quantitative description and figures were conducted by MY and YXS with Microsoft Excel 2016 (product ID: 00334-39022-77892-AA911) and the GraphPad Prism 6 (serial number: GPW6-811517-RJJH-C213A).

Results

Basic information of registered studies

After searching on the registries, 406 records were retrieved and after removing duplicates, 393 were eligible and included in the analysis. 321 studies were from ChiCTR, 69 from the Clinicaltrials.gov, and 3 from Japanese Registry. No records were found from other registries.

The countries hosting the trials were China (380 studies), Japan (3), France (3), the US (2), and other three international collaboration studies (2 studies with no country origin) (Supplementary Fig. 1). Among those 380 studies in China, 36 studies were supposed to be conducted in more than 2 provinces, and 328 studies each in one province (26 provinces in total) except 16 studies with no information about the place. One study was an online survey investigating quality of life of Chinese residents during or after the outbreak of new coronavirus pneumonia (COVID-19).

Figure 1 demonstrates the trend of confirmed cases (COVID-19) in China, and the number of registered studies. From the date of first trial registered to March 3, the number of confirmed cases was increasing and reached 59084 on March 3. Meanwhile the number of registered studies were also increased to 393, with a daily number of registrations range from 1 to 20.

In total, there were 198 institutions planning the studies on COVID-19 worldwide, and 22 had registered for more than 4 studies (Supplementary Fig. 2) (10 with missing information). Tongji Hospital of Tongji Medical College at Huazhong University of Science and Technology was on the top of the rank with 18 registrations, the second were West China Hospital of Sichuan University, and the First Hospital Affiliated to Zhejiang University's Medical School, registered 12 studies, respectively.

Study design of registered studies

Table 1 shows the characteristics of the included studies. Of the 393 studies, 266 were therapeutic studies (67.7%). In the 266 studies, 184 were RCTs, followed by 27 controlled clinical trials. In addition to the prevention, diagnosis, and prognosis studies, 67(17.0%) had other aims shown in the notes of Table 1. There were 202 (51.4%) RCTs. Among them, one was using an adaptive design testing remdesivir. The anticipated start date or the study execution time and registration date on the registrations were compared in RCTs, and 95 of them started the studies before registration, indicating retrospective registrations.

312 small sample size (less than 300) studies made up 79.4% of the registered studies. The average sample size was 1061 and ranged from 8 to 150,000 per study. The population included in studies were mainly confirmed COVID-19 patients, accounting for 78.4% (308 studies), and other populations such as people exposed to patients, suspected infection cases, the combined participants of confirmed and suspected infection cases, rehabilitation people and other disease without COVID-19 were also involved in the registered studies (85 studies, 21.6%). 179 studies (45.5%) had not started recruiting on Mar 3, 192 studies (48.9%) were recruiting and one study on eculizumab was on expanded access. The three completed studies were cohort study for therapeutic effect, cross-sectional study for the psychological status investigation, and the prognosis study of computerized tomography score predicting mortality.

As of retrieval, 268 studies (68.2%) registered on ChiCTR attached the ethical approval documents and 62 studies (15.8%) didn’t. The ethical approval information could not be checked for 63 other studies (16.0%) registered on clinicaltrials.gov or Japanese Registries.

The interventions and comparisons of 266 therapeutic studies are shown in Table 1. 177 studies (66.5%) were testing Western medicine and others were for Chinese medicine (16 studies, 6.0%) or integrative therapy of both (73 studies, 27.4%). In terms of the comparisons, 122 therapeutic studies (45.9%) used conventional therapy as control intervention, claiming following to the guidance issued by National Health Commission and National Administration of Traditional Chinese Medicine. Antiviral drugs, placebo, blank, multiple controls, and others were the comparisons used in the studies (Table 1).

Western medicine

The therapeutic clinical trials contributed the largest proportion in the registrations with the number of 266 studies (Table 2). Among the tested Western medicine, 47 studies tested on antivirals including arbidol, lopinavir-ritonavir, darunavir, interferon, ribavirin, and danoprevir. Apart from these antivirals in China, five RCTs registered for remdesivir, including two phase randomized, double-blind, placebo-

controlled multicenter study for mild/moderate and severe patients, two phase RCTs comparing different duration with standard therapy, and one phase multicenter, adaptive, randomized blinded controlled trial. Other trials tested antivirals not marketed in China including fapilavir, xofluza, azvudine, triazavirin, and ASC09F.

Other tested Western treatments included stem cell and cord blood (27 studies), chloroquine and derivatives (22 studies), immunological agents and monoclonal antibodies (15 studies), convalescent plasma therapy (8 studies), inhalation therapy of oxygen, nitric oxide, and hydrogen-oxygen (6 studies), glucocorticoids (6 studies), psychological therapy (4 studies), vitamins (3 studies), and extracorporeal membrane oxygenation (ECMO) (2 studies).

There were 8 studies for COVID-19 prevention testing Western medicine, such as arbidol, interferon spray, hydroxychloroquine and mask for doctors during gastroscopy. These studies had not started recruitment according to the registrations.

Traditional Chinese medicine and their rationale

The secondary category of interventions was Chinese medicine (16 studies) and integrated therapies of multiple drugs and non-pharmaceutical interventions (73 studies). Except for 46 studies using Chinese medicines without detailed information, and one tested Chinese medicine granule for people with common cold, other involved Chinese medicines, compositions and rationale in 34 studies are presented in Table 3. 14 Chinese medicines had evidence on COVID-19 or related diseases (acute upper respiratory tract infections, acute bronchitis, pneumonia, influenza) or symptoms *in silico*, *in vitro*, *in vivo* and in human level such as expert consensus statement, RCTs, systematic reviews, and overview. The non-pharmaceutical Chinese therapies included acupuncture (1 trial), massage (tuina) in children (1 study), moxibustion (1 study), emotional therapy (1 trial), different styles of Qigong such as Dao-yin (1 trial), acupressure combined with Liuzijue Qigong (1 trial), Baduanjin (1 trial), integrative exercises for lung function recovery (1 trial), fitness Qigong Yangfei prescription (1 trial), and Guixi Tiao Fei Gong method (1 trial). Moxibustion (a traditional used therapy) was recommended by the Guidance on acupuncture for COVID-19 by China Association of Acupuncture-Moxibustion, and acupuncture should be combined with Western medicine [21]. The functional recovery of integrated therapy such as Taichi, Baduanjin, Wuqinxi exercise, Liuzijue qigong, Yijinjing were recommended by the research team from Shanghai University of Chinese Medicine [22].

Except for trials on therapeutic effect, Chinese medicine was also tested for the prevention and rehabilitation of coronavirus patients. For prevention, the tested herbal therapies included Jinhao Jiere granule, Gubiao Jiedu Ling, Jinye Baidu granule, Kangbingdu oral liquid, Compound *Houttuyniae Herba*, and moxibustion. For rehabilitation, Taichi was tested for pulmonary function and quality of life in COVID-19 patients at convalescent stage (1 trial), and integrated exercises for lung function recovery were tested in survivors of COVID-19 (1 observational study). Besides, emotional therapy of Chinese medicine was tested for novel coronavirus patients and nurses (1 trial).

Outcomes of the registered studies

In Table 4, only 17 RCTs, 2 controlled clinical trials, and 12 observational studies (31 studies totally, 11.7%) used mortality as a primary outcome. Other clinical important outcomes such as exacerbation rate/time (26 studies, 9.8%) and length of intensive care unit (ICU) stay (2 studies, 0.8%) were also seldom used as primary outcomes. Symptoms and signs were listed in 105 studies (39.5%) as primary outcomes, while 125 studies (47.0%) as secondary outcomes. Common laboratory parameters were used in 40 studies (15.0%) as primary outcomes, while 109 studies (41.0%) as secondary outcomes.

Trials identified as the most promising clinical trials

Totally 8 RCTs were judged as the most promising trials for the treatment of COVID-19, which were RCTs for therapeutic effects with clear and available intervention, primary outcomes with mortality or exacerbation, and potential human evidence for the treatment of COVID-19 (Table 5). Four of them had direct evidence on the treatment of COVID-19 patients and others had evidence on H7N9, severe community-acquired pneumonia, and sanitation workers.

Discussion

This study systematically reviewed available registered studies for COVID-19 with the analyses of their distributions and characteristics. 393 studies were registered in eight registries, aiming at the prevention (16 studies), treatment (266), diagnosis (25) and prognosis (19) of COVID-19. Majority of the studies were randomized trials, followed by observational studies testing different interventions such as antiviral drugs, Chinese medicine, and integrated therapies. Except for 50 studies, clinical important outcomes such as mortality and exacerbation rate/time were not set as primary outcomes in majority trials. 179 studies had not started recruiting and would hardly be able to carry on in China due to insufficient patients.

As a new communicable disease, direct evidence for the prevention of COVID-19 is not available. We found insufficient evidence to support the rationale for tested Western medicines, while based on historical records and human evidence of SARS and H1N1 influenza prevention, Chinese herbal formula is considered as an alternative approach for prevention of COVID-19 in high-risk population [29]. The therapeutic clinical studies made up the largest proportion of the registrations. Antivirals, the most promising category of Western medicine, accounted for 17.7% out of the therapeutic studies. Eight RCTs were identified as promising trials under the criteria of study design and related human evidence. In terms of Chinese medicines, 14 had clinical or laboratory evidence, showing the potential therapeutic effects on COVID-19 patients.

Flaws in study design, such as the setting of the control and outcomes, and the lack of coordination were discovered from the registrations. Even in an outbreak, investigational products should be evaluated in scientifically and ethically sound studies [30]. *Do no harm* is always the first rule for all human studies. Methodologically, double-blind randomized, placebo controlled trials are considered to be the gold standard for therapeutic clinical trials [31]. However, considering the emergency and the practical issues

of ethics and informed consent, the implementation of RCT faces more challenges. In the context of COVID-19 pandemic, the control interventions should be supportive care.

As statistics shows, the mortality of COVID-19 was 4.3% in Wuhan, China, indicating severe life-threatening disease [32]. New studies on clinical characteristics of COVID-19 also reported outcomes on exacerbation, such as the median time from first symptom to dyspnea, acute respiratory distress syndrome (ARDS), transfer to the intensive care unit (ICU) due to complications and death of multiple organ failure [32, 33], and other symptoms and laboratory findings for example neutrophilia, organ and coagulation dysfunction, which were potential risk factors for ARDS [34] and elevated d-dimer as risk factors for mortality [35]. On the contrary, clinical important outcomes such as mortality and exacerbation were only used as primary outcomes in 21.5% analyzed registrations, and the observational measures in clinical practice such as symptoms, signs, common laboratory tests and viral nucleic acid/viral load were used more frequently. What's more, the most used primary and secondary outcomes were similar and clear measurements and time points were seldom available. The design of more than three primary outcomes in one trial may bring problems in the interpretation of research results [6].

Although the number of registered trials is increasing, only carefully conducted trials can show which measures work [36]. Without a coordination of the research teams in the whole country, potential participants could be scattered in numerous small studies, resulting in less powerful results or incomplete trials. There were only 3 international and 36 domestic collaboration studies, suggesting a low level of cooperation. In fact, the registrations showed that nearly half of the studies had not started recruiting by Mar 3, while the new cases in China were sharply reducing. Besides, a few of the sponsors had withdrawn their studies due to lack of patients. In fact, we could learn from the experience on study design of Ebola virus disease according to WHO documents [31, 37]. For example, the adaptive trial designs were used in the Ebola epidemic, it has the capacity to yield meaningful and interpretable data quickly, while more complex to coordinate among different sites. The key points of study design in these documents may also helpful for the design and implementation of COVID-19 clinical trials.

There are several limitations in our research. First, the registrations provide limited information on the trials, and our analysis is based on the registered information but not the full protocols. Second, the required information of the registrations are not unique across different registries, and the information could be revised by sponsors after the search and analysis, so the results may not include the whole registered information of the COVID-19 studies. Third, the criteria of the most promising trials were based on the authors' consensus but not a widely used standard, we still look forward to more encouraging results of the registered trials not limited to the identified ones.

More international collaborations, rapid data sharing, and strengthened coordination are needed in the searching for effective therapy. As WHO suggested, enhancing global coordination of all relevant stakeholders, a clear and transparent global research and innovation priority setting and common platforms for standardized process are needed in the research during the outbreak [38]. In addition, WHO and partners are launching SOLIDARITY trial and aims to generate robust data for the most effective

treatment for COVID-19 [3]. In addition, rapid data sharing is warranted once they are adequately quality controlled for release [39]. To response the outbreak of COVID-19, a quick upload of data is recommended when registered trials initiated so for immediate analysis and inform upcoming trials. Thirdly, the coordination of the trials are urgently needed. More rigorous regulations by the National Health Commission in China have been delivered for the clinical studies on COVID-19 recently, aim to strengthen overall coordination, promote data integration, and improve research efficiency [40]. With the statistics of registered information, we will trace the trials for the update status regularly. Further research could be conducted to investigate the impact factors of a successful trial in the emergency of public events, and summarize valuable experience for the protocols of unexpected emergency events.

Conclusion

From Jan 23 to Mar 3 2020, 393 studies were registered for the prevention, treatment, diagnosis and prognosis of COVID-19. The limitations of design, delayed recruitment, and insufficient numbers of new cases in China make studies difficult to complete. International collaborations are important to achieve efficient research on global pandemics, and robust and rapid data sharing is urgently needed. Research protocols for public health emergency will be warranted and priority trials could be defined in shorter time, avoiding the waste of resources and duplication of research efforts.

Abbreviations

2019-nCoV, COVID-19, SARS-CoV-2: coronavirus disease 2019; ARDS: acute respiratory distress syndrome; CCT: controlled clinical trial; ChiCTR: Chinese clinical trial registry; ECMO: Extracorporeal Membrane Oxygenation; HIV: human immunodeficiency virus; ICU: intensive care unit; MERS: Middle East respiratory syndrome; NA: not available; RCT: randomized controlled trial; SARS: severe acute respiratory syndromes; TCM: traditional Chinese medicine; US: United States of America; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated and analysed during this study are included in this article.

The included trials were published on the open access website and databases.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

MY, Ying Zhang and JPL conceived and carried out the study. MX, YJ, Yao Zhang, YYZ, YXS, ZYT, XYJ and QBJ undertook the data extraction. YXS assisted in the statistical analysis. CLL, ZYT and MY drafted the manuscript. Ying Zhang, JPL and MW revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 The characteristics of the registered studies from eight registries

Items	Details	n	%
Aim	Prevention	16	4.1
	Therapeutic evaluation	266	67.7
	Diagnosis	25	6.4
	Prognosis	19	4.8
	Others	67	17.0
Setting	Hospital	363	92.4
	Community	4	1.0
	Others (university, online and research institute)	3	0.8
	NA	23	5.9
Study type	RCTs	202	51.4
	CCTs	31	7.9
	Single arm trials	23	5.9
	Observational studies	96	24.4
	Cross-sectional studies	16	4.1
	Diagnostic tests	18	4.6
	Others (basic science/factorial/NA)	7	1.8
Sample size	≤100	206	52.4
	101-300	106	27.0
	301-500	43	10.9
	501-1500	21	5.3
	1500+	14	3.6
	NA	3	0.8
Populations	People exposed to patients	38	9.7
	Suspected infection	9	2.3
	Confirmed or suspected infection	15	3.8
	Mild or moderate	121	30.8
	Moderate or severe	6	1.5
	Severe or critical illness	72	18.3
	Confirmed patients (without details for stage or all stages included)	96	24.4
	Confirmed patients with complications	7	1.8
	Rehabilitation	9	2.3
	Special population (children, neonates, women, maternal)	6	1.5
	Other diseases without COVID-19	6	1.5
	Others	8	2.0
Recruitment status	Not yet recruiting	179	45.5
	Recruiting	192	48.9
	Completed	4	1.0
	Suspended	3	0.8
	Expanded access	1	0.3
	NA	14	3.6
Interventions (therapeutic studies)	Western medicine	177	66.5
	Chinese medicine	16	6.0
	Integrated therapy	73	27.4
Comparisons (therapeutic studies)	Conventional therapy	122	45.9
	Antiviral drugs	26	9.8
	Placebo	28	10.5
	Blank	11	4.1
	No control group	47	17.7

	Multiple controls	14	5.3
	Others	18	6.8
Funding source	Government	106	27.0
	Hospital	74	18.8
	University/Research institute/Academic association	22	5.6
	Multiple funding	18	4.6
	Industry	44	11.2
	Self-raised	105	26.7
	No funding	7	1.8
	NA	17	4.3
Ethical approval	Yes	268	68.2
	Unclear	125	31.8

Note:

NA: not available;

Other aims: epidemiology research, description of clinical or imaging characteristics, investigation on traditional Chinese medicine (TCM) syndrome;

RCT: randomized controlled trial; CCT: controlled clinical trial;

Other populations: health or suspected infectious people, COVID-19 patients and other types of pneumonia, COVID-19 patients and other influenza patients;

Expanded access: currently available for this investigational treatment, and patients who are not participants in the clinical study may be able to gain access to the drug, biologic, or medical device being studied;

Other comparisons: different dosage or duration of the tested intervention, “historical comparison” (without details), γ-Globulin, bag-valve mask oxygenation Assisted tracheal intubation, psychological intervention (without details), Chinese medicine.

Table 2 Categories of Western medicine and Chinese medicine in the registered studies

Intervention	Category	n	%
Western medicine	Antiviral drugs	47	17.7
	Stem cell and cord blood therapy	27	10.2
	Chloroquine and derivatives	22	8.3
	Immunology and monoclonal antibodies	15	5.6
	Convalescent plasma	8	3.0
	Inhalation therapy	6	2.3
	Glucocorticoids	6	2.3
	Psychological therapy	4	1.5
	Vitamins	3	1.1
	ECMO	2	0.8
	Others	36	13.5
Chinese medicine	CM with no details	46	17.3
	Patent herbal drugs	17	6.4
	Herbal injections	10	3.8
	Non-pharmaceutical intervention	9	3.4
	Herbal decoctions	6	2.3
	Multiple Chinese medicine therapy	2	0.8

Note: ECMO: Extracorporeal Membrane Oxygenation; TCM: Traditional Chinese Medicine

Due to technical limitations, Table 3 is only available as a download in the supplemental files section

Table 4 Primary and secondary outcomes measured in the registered studies on therapeutic effect evaluation

Outcomes	No. of studies indicated as primary outcomes (%)	No. of studies indicated as secondary outcomes (%)
Mortality	31 (11.7)	67 (25.2)
Exacerbation rate/time	26 (9.8)	62 (23.3)
Length of stay in ICU	2 (0.8)	25 (9.4)
Length of hospital stay	20 (7.5)	58 (21.8)
Cure rate	23 (8.7)	17 (6.4)
Discharge rate	6 (2.3)	4 (1.5)
Lung function	28 (10.5)	30 (11.3)
Mechanical ventilation and oxygen inhalation time/rate	12 (4.5)	52 (19.6)
Imaging examinations (chest CT, X radiograph, etc.)	47 (17.7)	43 (16.2)
Oxygenation indicator	29 (10.9)	28 (10.5)
Symptoms and signs	105 (39.5)	125 (47.0)
Health status/mental state/quality of life	9 (3.4)	18 (6.8)
Viral nucleic acid/viral loads	76 (28.6)	86 (32.3)
Common laboratory tests (blood, urine routine, biochemicals, etc.)	40 (15.0)	109 (41.0)
Safety (adverse events/adverse drug reactions, etc.)	18 (6.8)	67 (25.2)
Complications	4 (1.5)	10 (3.8)
TCM Syndrome score	11 (4.1)	12 (4.5)
Other outcomes	12 (4.5)	17 (6.4)

Note: CT: computerized tomography; ICU: Intensive care unit; TCM: Traditional Chinese Medicine; Viral loads: changes of real-time reverse-transcriptase-polymerase-chain-reaction testing.

Table 5 Characteristics of trials judged as promising

Registration date	Title (Registration number)	Study design	Treatment being tested	Population	Sample size	Setting	Recruiting status	Primary Outcomes	Rationale
2020-2-7	Clinical Study for Human Menstrual Blood-Derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) (ChiCTR2000029606)	RCT	Intravenous infusion of Human Menstrual Blood-derived Stem Cells preparations; Artificial liver therapy	Severe and critical illness	63	The First Affiliated Hospital, College of Medicine, Zhejiang University (Tertiary A hospital)	Recruiting	Mortality in patients	CCT: The controlled clinical trial of mesenchymal stem cell treatment significantly lowered the mortality of acute respiratory distress syndrome induced by epidemic influenza A (H7N9) infection [23].
2020-2-11	A Multicenter, Randomized, Parallel Controlled Clinical Study of Hydrogen-Oxygen Nebulizer to Improve the Symptoms of Patients With Novel Coronavirus Pneumonia (COVID-19) (ChiCTR2000029739)	RCT	Hydrogen-Oxygen Nebulizer	moderate and severe	440	3 tertiary hospitals located in Guangzhou and Shanghai, China	Recruiting	The condition worsens and develops into severe or critical condition, the condition improves significantly and reaches the discharge standard, the overall treatment time	Quasi-RCT: The inhalation of hydrogen-oxygen or hydrogen was tested in sanitation workers, and it was shown alleviation of airway inflammation and oxidative stress [24].
2020-2-11	Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study (ChiCTR2000029741)	RCT	Chloroquine Phosphate; Lopinavir / Ritonavir	Mild and moderate	112	The Fifth Affiliated Hospital Sun Yat-Sen University (Tertiary A Hospital in Guangdong, China)	Recruiting	Length of stay, length of severe, oxygenation index during treatment, all-cause mortality in 28 days, peripheral blood cell count, procalcitonin, C-reactive protein, inflammatory factors, lymphocyte subsets and complement, Coagulation indicators, virus nucleic acid	RCT: the body temperature recovery time and the cough remission time were significantly shortened and the absorption of pneumonia was improved in the group with additional treatment of hydroxychloroquine [25].
2020-2-24	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19) (ChiCTR2000030179)	RCT	plasma treatment	Severe	100	The First Affiliated Hospital of Nanchang University (Tertiary A Hospital in Jiangxi, China)	Recruiting	Cure rate, mortality	Single arm trial: The results from 10 severe COVID-19 cases showed that one dose (200 mL) of convalescent plasma was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level, leading to disappearance of viremia in 7 d. Meanwhile, clinical symptoms and paraclinical criteria rapidly improved within 3

									d. Radiological examination showed varying degrees of absorption of lung lesions within 7 d [26].
2020-2-24	Clinical study for Lopinavir and Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) (ChiCTR2000030187)	RCT	Lopinavir and Ritonavir Tablets	Confirmed patients	60	Jingzhou first people's Hospital (Tertiary A Hospital in Hubei, China)	Recruiting	Endotracheal intubation rate, mortality	RCT: Lopinavir and ritonavir on COVID-19 patients showed no benefit in mortality at 28 days and the time to clinical improvement [27], while a better effect could be expected for mild and moderate patients.
2020-2-26	A multicenter, randomized, controlled trial for efficacy and safety of hydrogen inhalation in the treatment of novel coronavirus pneumonia (COVID-19) patients (ChiCTR2000030258)	RCT	hydrogen inhalation	Confirmed patients	60	4 Tertiary A hospitals in Heilongjiang, China	Not yet recruiting	Fatality rate, temperature, respiratory rate, blood oxygen saturation, cough symptom, lung CT	Quasi-RCT: The inhalation of hydrogen-oxygen or hydrogen was tested in sanitation workers, because it was shown alleviation of airway inflammation and oxidative stress [24].
2020-3-1	Efficacy and safety of Xue-Bi-Jing injection in the treatment of severe cases of novel coronavirus pneumonia (COVID-19) (ChiCTR2000030388)	RCT	Xuebijing injection	Severe	60	Jingzhou First People's Hospital (Tertiary A hospital in Hubei, China)	Recruiting	The percentage of patients who convert to moderate, The rate of shock, Endotracheal intubation ratio, Time spent on the ventilator, mortality, Time of virus nucleic acid test turning negative	RCT: Significant improvement in the pneumonia severity index, mortality, duration of mechanical ventilation, and duration of ICU stay were observed for critically ill patients with severe community-acquired pneumonia [14].
2020-2-21	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (NCT04280705)	RCT	Remdesivir	Confirmed patients	394	20 study locations worldwide	Recruiting	Percentage of subjects reporting each severity rating on an 8-point ordinal scale	Cohort study: patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy[28].

Notes:

RCT: randomized controlled trial; CCT: controlled clinical trial; SR: systematic review; ICU: Intensive care unit.

Figures

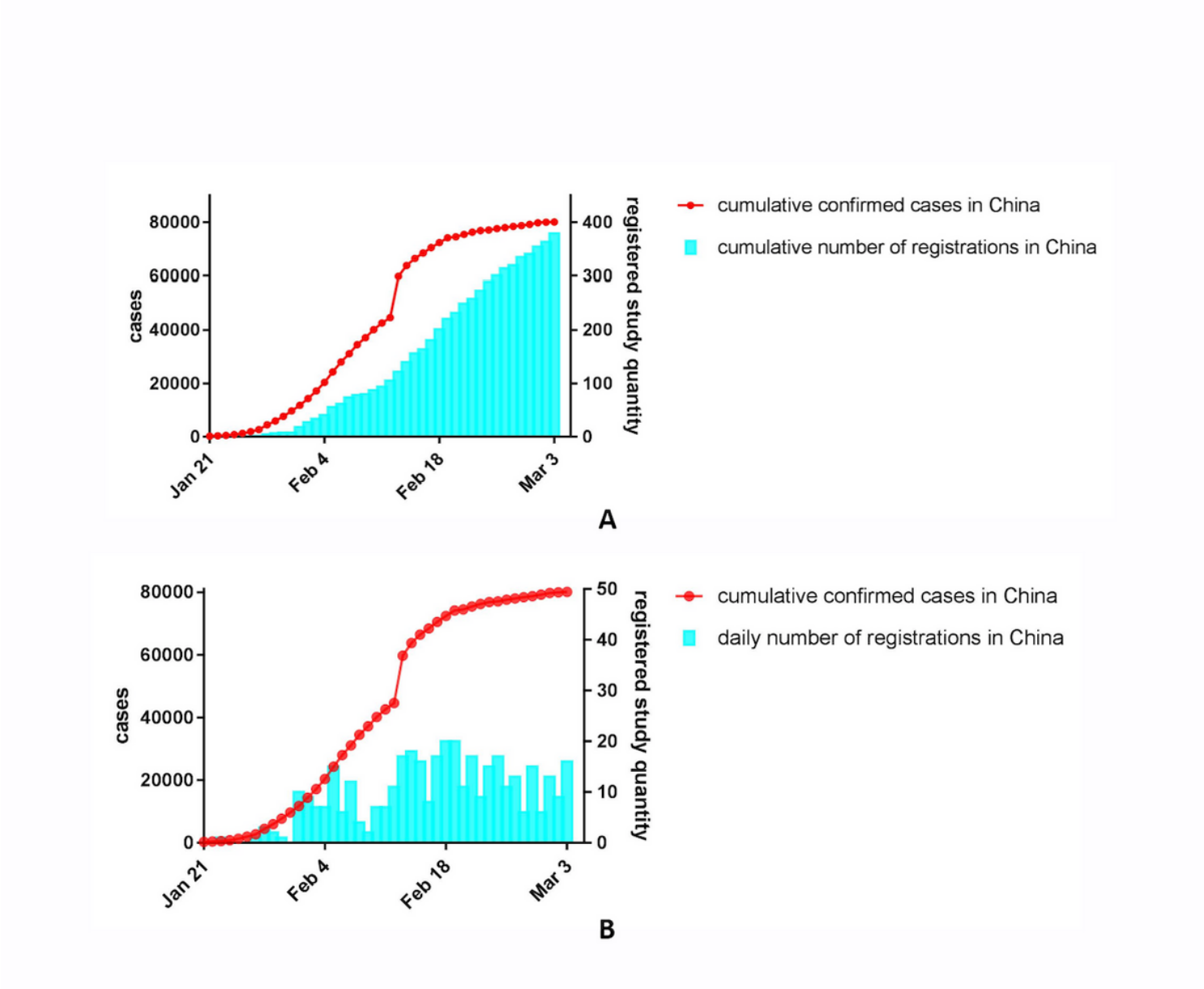

Figure 1

Cumulative confirmed COVID-19 cases along with cumulative number of registered studies and daily registrations in China

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tif
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- SupplementaryFigure2.tif
- Table3.docx
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