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 III randomized, double-blind, placebo-controlled multicenter study for mild/moderate and severe patients, two phase III RCTs comparing different duration with standard therapy, and one phase II 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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**References**

1. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-92.

2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia [published online ahead of print, 2020 Jan 29]. N Engl J Med. 2020;10.1056/NEJMoa2001316.

3. Coronavirus (COVID-19). events as they happen. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed 26 March 2020.
4. Coronavirus, Update (Live). https://www.worldometers.info/coronavirus. Accessed 30 March 2020.

5. Premier Li Keqiang presided over a meeting of the Central Leading Group for New Coronavirus Epidemic. Situation, deployed further classification, effective prevention and control, required optimization of diagnosis and treatment, and accelerated scientific research on drug control. http://www.gov.cn/premier/2020-02/13/content_5478410.htm. Accessed 26 March 2020.

6. Wei X, Zhao M, Zhao C, Zhang X, Qiu R, Lin Y, et al. The global registry of COVID-19 clinical trials: indicating the design of traditional Chinese medicine clinical trials. TMR Modern Herbal Medicine 2020.online. doi: 10.12032/TMRmhm202003068.

7. Prevention and control of new coronavirus pneumonia.
http://www.nhc.gov.cn/xcs/xxgzb/gzbd_index.shtml. Accessed 26 March 2020.

8. Li R, Hou Y, Huang J, Pan W, Ma Q, Shi Y, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2) [published online ahead of print, 2020 Mar 20]. Pharmacol Res. 2020;104761.

9. Yao Y, He Z, Liu X, He Y, Lei Y, Zhang S, et al. Potential material basis of Kangbingdu Keli for the treatment of coronavirus pneumonia 2019 (COVID-19) based on network pharmacology and molecular docking technology. Chinese Traditional Herbal Drugs. 2020;51(6):1386–96. doi:10.7501/j.issn.0253-2670.2020.06.003.

10. Jin J, Lv J, Wang Z, Xie Y, Sun M. Effectiveness and Safety of Ganke Shuangqing Capsule for Acute Upper Respiratory Tract Infection: A Systematic Review and Meta-analysis. World Chinese Medicine. 2020;15(01):24–9. doi:10.3969/j.issn.1673-7202.2020.01.005.

11. Zhao R, Sun J, Shi Y, Bao L, Geng Z, Guo S, et al. Intervening Effect of Promoting Lung and Resolving Phlegm Method on a Mouse Model Combining Disease and
Syndrome of Human Coronavirus Pneumonia with Cold-dampness Pestilence Attacking Lung. Chinese Journal of Experimental Traditional Medical Formulae. 2020;1–7; doi:10.13422/j.cnki.syfjx.20201149.

12. Tang Y, Wang Z, Huo C, Guo X, Yang G, Wang M, et al. Antiviral effects of Shuanghuanglian injection powder against influenza A virus H5N1 in vitro and in vivo. Microb Pathog. 2018;121:318–24.

13. Luo J, Song W, Yang G, Xu H, Chen K. Compound Danshen (Salvia miltiorrhiza) dripping pill for coronary heart disease: an overview of systematic reviews. Am J Chin Med. 2015;43(1):25–43.

14. Song Y, Yao C, Yao Y, Han H, Zhao X, Yu K, et al. XueBijing Injection Versus Placebo for Critically Ill Patients With Severe Community-Acquired Pneumonia: A Randomized Controlled Trial. Crit Care Med. 2019;47(9):e735–43.

15. Wang P, Liao X, Xie YM, Chai Y, Li LH. Tanreqing injection for acute bronchitis disease: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2016;25:143–58.

16. Liu Y, Mu W, Xiao W, Wei B, Wang L, Liu X, et al. Efficacy and safety of Re-Du-Ning injection in the treatment of seasonal influenza: results from a randomized, double-blinded, multicenter, oseltamivir-controlled trial. Oncotarget. 2017;8(33):55176–86.

17. Wang Z, Zhang H, Xie Y, Miao Q, Sun Z, Wang R, et al. Expert consensus statement on Xiyanping Injection for respiratory system infectious diseases in clinical practice (adults). China Journal of Chinese Materia Medica. 2019;44(24):5282–6. doi:10.19540/j.cnki.cjcm.20191105.502.

18. Lv SJ, Lai DP, Wei X, Yan Q, Xia JM. The protective effect of Shenfu injection against elderly severe pneumonia. Eur J Trauma Emerg Surg. 2017;43(5):711–5.

19. Zhou Z, Li X, Liu J, Dong L, Chen Q, Liu J, et al. Honeysuckle-encoded atypical
20. Wang C, Cao B, Liu Q, Zou Z, Liang Z, Gu L, et al. Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial [published correction appears in Ann Intern Med. 2012 Jan 3;156(1 Pt 1):71]. Ann Intern Med. 2011;155(4):217–225.

21. Guidance on Acupuncture intervention for COVID-19 by China Association of Acupuncture-Moxibustion. http://www.caam.cn/article/2183-. Accessed 26 March 2020.

22. Liu X, Liu L, Lu Y, Feng L, Zhao F, Wu X, et al. Guidance and suggestions on rehabilitation training of integrated traditional Chinese and western medicine for functional recovery of patients with novel coronavirus pneumonia. Shanghai Journal of Traditional Chinese Medicine. 2020;54(03):9–13. doi:10.16305/j.1007-1334.2020.03.003.

23. Chen J, Hu C, Chen L, Tang L, Zhu Y, Xu X, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection: a hint for COVID-19 treatment. Engineering. 2020. doi:10.1016/j.eng.2020.02.006.

24. Gong Z, Guan J, Ren X, Meng D, Zhang H, Wang B, et al. [Protective effect of hydrogen on the lung of sanitation workers exposed to haze]. Zhonghua Jie He He Xi Za Zhi. 2016;39(12):916–23. doi:10.3760/cma.j.issn.1001-0939.2016.12.003.

25. 10.1101/2020.03.22.20040758v3

Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Preprint at https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3.

26. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma
therapy in severe COVID-19 patients [published online ahead of print, 2020 Apr 6]. Proc Natl Acad Sci U S A. 2020;202004168.

27. 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 [published online ahead of print, 2020 Mar 18]. N Engl J Med. 2020;10.1056/NEJMoa2001282.

28. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19 [published online ahead of print, 2020 Apr 10]. N Engl J Med. 2020;10.1056/NEJMoa2007016.

29. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, et al. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs [published online ahead of print, 2020 Feb 17]. Chin J Integr Med. 2020;1–8.

30. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted [published online ahead of print, 2020 Feb 28]. N Engl J Med. 2020;10.1056/NEJMe2002387.

31. WHO. Ethical issues related to study design for trials on therapeutics for Ebola virus disease. https://www.who.int/csr/resources/publications/ebola/ethical-evd-therapeutics/en. Accessed 26 March 2020.

32. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7]. JAMA. 2020;e201585.

33. Chang D, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, et al. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China [published online ahead of print, 2020 Feb 7]. JAMA. 2020;323(11):1092–3.

34. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al: Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019
Pneumonia in Wuhan, China [published online ahead of print, 2020 Mar 13]. JAMA Intern Med. 2020;e200994.

35. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published online ahead of print, 2020 Mar 11] [published correction appears in Lancet. 2020 Mar 12;:]. Lancet. 2020;S0140-6736(20)30566-3.

36. Maxmen A. Slew of trials launch to test coronavirus treatments in China. Nature. 2020;578:347–8.

37. WHO: Consultation on Clinical Trial Design for Ebola Virus Disease. https://www.who.int/csr/resources/publications/ebola/consultation-clinical-trial-design-ebola/en. Accessed 26 March 2020.

38. WHO. 2019 Novel Coronavirus (2019-nCoV): Strategic preparedness and response plan for the new coronavirus. https://www.who.int/publications-detail/strategic-preparedness-and-response-plan-for-the-new-coronavirus. Accessed 26 March 2020.

39. WHO. managing ethical issues in infectious disease outbreaks. https://www.who.int/ethics/publications/infectious-disease-outbreaks/en. Accessed 26 March 2020.

40. Letter of the joint prevention and control mechanism of the State Council on notice on standardizing medical. institutions to carry out clinical research on new coronavirus pneumonia drug treatment. http://www.most.gov.cn/tztg/202004/t20200403_152882.htm. Accessed 6 April 2020.

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   |
| Setting                                      | Prognosis | Others  |
|----------------------------------------------|-----------|---------|
| Hospital                                     | 19        | 4.8     |
| Community                                    | 67        | 17.0    |
| Others (university, online and research institute) | 4         | 1.0     |
| NA                                          | 23        | 5.9     |

| Study type                                   | Prognosis | Others  |
|----------------------------------------------|-----------|---------|
| 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                                  | Prognosis | Others  |
|----------------------------------------------|-----------|---------|
| ≤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                                  | Prognosis | Others  |
|----------------------------------------------|-----------|---------|
| 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                           | Prognosis | Others  |
|----------------------------------------------|-----------|---------|
| 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)          | Prognosis | Others  |
|----------------------------------------------|-----------|---------|
| Western medicine                             | 177       | 66.5    |
### Comparisons (therapeutic studies)

| Category                               | Count | Percentage |
|----------------------------------------|-------|------------|
| Chinese medicine                        | 16    | 6.0        |
| Integrated therapy                      | 73    | 27.4       |
| Conventional therapy                   | 122   | 45.9       |

| Category                      | Count | Percentage |
|-------------------------------|-------|------------|
| 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

| Source                                   | Count | Percentage |
|------------------------------------------|-------|------------|
| 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

| Status  | Count | Percentage |
|---------|-------|------------|
| 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  | 1  |
|                                     | Stem cell and cord blood therapy| 27  | 1  |
|                                     | Chloroquine and derivatives      | 22  | 8  |
|                                     | Immunology and monoclonal antibodies | 15  | 5  |
|                                     | Convalescent plasma              | 8   | 3  |
|                                     | Inhalation therapy               | 6   | 2  |
|                                     | Glucocorticoids                  | 6   | 2  |
|                                     | Psychological therapy            | 4   | 1  |
|                                     | Vitamins                         | 3   | 1  |
|                                     | ECMO                             | 2   | 0  |
|                                     | Others                           | 36  | 1  |
| Chinese medicine                    | CM with no details               | 46  | 1  |
|                                     | Patent herbal drugs              | 17  | 6  |
|                                     | Herbal injections                 | 10  | 3  |
|                                     | Non-pharmaceutical intervention   | 9   | 3  |
|                                     | Herbal decoctions                 | 6   | 2  |
|                                     | Multiple Chinese medicine therapy | 2   | 0  |

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
| 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 size | Sample setting | Recruiting status | Prim: Outc |
|-------------------|-----------------------------|--------------|------------------------|-----------------|-----------------|-------------------|------------|
| 2020-2-7          | Clinical Study for Human Menstrual Blood-Derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia | RCT | Intravenous infusion of Human Menstrual Blood-derived | 63 | The First Affiliated Hospital, College of Medicine, Zhejiang University (Tertiary A hospital) | Recruiting | Mort: patie |
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)

Hydrogen-Oxygen Nebulizer

RCT

Moderate and severe

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

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)

Chloroquine Phosphate; Lopinavir / Ritonavir

RCT

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, cause mortality in 28 days, peripheral blood cell count, procalcitonin, C-reactive protein, inflammatory factors, cytotoxic subsets and complement, Coagulation indicators, virus nucleic acid

2020-2-24 Experimental study of novel coronavirus (COVID-19) plasma treatment (ChiCTR2000029606)

Stem Cells preparations; Artificial liver therapy

RCT

Severe

100

The First Affiliated Hospital of Recruiting

Cure mort
pneumonia rehabilitation
plasma therapy severe
coronavirus
pneumonia (COVID-19)

(ChiCTR2000030179)

Nanchang
University (Tertiary
A Hospital in Jiangxi,
China)

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2020-2-24
Clinical study for
Lopinavir and Ritonavir in
the treatment of novel
coronavirus pneumonia
(COVID-19)
(ChiCTR2000030187)

2020-2-24
Clinical study for
Lopinavir and Ritonavir in
the treatment of novel
coronavirus pneumonia
(COVID-19)
(ChiCTR2000030187)

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)

2020-3-1
Efficacy and safety of
Xue-Bi-Jing injection in the
treatment of severe cases
of novel coronavirus
pneumonia (COVID-19)
(ChiCTR2000030388)
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)

2020-2-21

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
SupplementaryFigure2.tif
Table3.docx