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Chinese clinical studies for pharmacological treatments of coronavirus disease 2019 (COVID-19)

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Abstract

Objectives

This study aims to identify, report, and analyze registered and published clinical trials and observational studies for the pharmacological treatment of COVID-19 conducted in China.

Methods

A strategic search was conducted via the Chinese Clinical Trial Registry to identify and extract clinical trials and observational studies registered and conducted in China for the pharmacological treatment of COVID-2019 between January 1st, 2020 and March 21st, 2020. This was further supplemented by searches conducted via the China National Knowledge Infrastructure (CNKI) database, the MEDLINE database, the World Health Organization (WHO) database, and MedRxiv and BioRxiv electronic platforms for preprint articles, published up until April 8th, 2020. Studies available in Chinese and English were included in the searches and extracted. A primary descriptive analysis was performed for registered clinical trials and observational studies identified in the Chinese Clinical Trial Registry based on the extraction of the following clinical study information: trial ID, planned date of enrollment, recruitment status, study design, population, sample size, intervention/exposure group, control /reference group, dosage, and primary outcomes. A secondary descriptive analysis was performed for published clinical trials and observational studies identified from the supplementary databases based on the extraction of the following published clinical study information: study design, population, intervention/exposure group, control /reference group and main results as appropriate.

Results

A total of 221 clinical trials and observational studies were included from all databases searched. From the Chinese Clinical Trial Registry, 195 registered clinical studies including 170 clinical trials and 25 observational studies were identified and included for primary analysis. From the supplementary databases, 26 published clinical studies including 8 clinical trials and 18 observational studies were included for secondary analysis. Of these 26 published clinical studies, 18 studies, including 3 clinical trials and 15 observational studies were identified from CNKI, 2 studies including 1 clinical trial and 1 observational study from MEDLINE, 2 including 1 clinical trials and 1 observational studies from the WHO database, and 4 including 3 clinical trials and 1 observational studies from MedRxiv and BioRxiv platforms. In the primary analysis, among the 170 clinical trials included from the Chinese Clinical Trial Registry, 101 investigated western medicines (WMs), while 15 investigated Traditional Chinese Medicines (TCMs), and 54 investigated a combination of TCMs and WMs. Among the 25 included observational studies from the Chinese Clinical Trial Registry, 2 investigated WMs, 2 investigated TCMs, and 21 investigated a combination of TCMs and WMs. The total number of exposed patients in all 195 clinical studies from the Chinese Clinical Trial Registry amounted to 24,500. In the secondary analysis, treatment with Lopinavir-ritonavir and treatment with Hydroxychloroquine was not associated with a difference from standard of care in the rate of RT-PCR negativity; treatment with a combination of Lopinavir-ritonavir, interferon α, and Lian-Hua-Qing-Wen capsule was found to significantly improve the effective rate of treatment compared with Interferon α combined with Lian-Hua-Qing-Wen capsule.

Conclusions

China is generating a massive source of evidence that is critical for defeating the COVID-19 pandemic. Not only the clinical experience, but also the scientific evidence should be shared with the global scientific community.

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Key words: COVID-19, clinical studies, China, clinical trials, observational studies

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1. Introduction

By the end of December 2019 China announced the identification of a new emerging viral condition [1], caused by a novel coronavirus. The virus was provisionally named 2019-coronavirus (2019-nCoV) [2]and then finally named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease, itself, has been officially named as Coronavirus Disease 2019 (COVID-19). Initially confined to the Hubei Province, a specific region of China, the virus spread outside of China to such an extent that on March 12th, 2020, the World Health Organization (WHO) declared a COVID-19 pandemic [3]. COVID-19 spread across Asia [4], followed by Europe, and finally reached the United States (US), spreading to a degree that led WHO to suggest the US as the new focal point of the pandemic [5]. In China, 82,230 patients have been identified as infected by SARS-COV-2 and 3,301 have died as of the 29th of March 2020[6]. The global mortality was estimated by WHO to be about 3.4% on March 3rd, 2020. By comparison, the seasonal flu generally kills far fewer than 1% of those infected [7]. Although the mortality is unknown as the denominator is impossible to assess the absolute number of deaths and the majority of patients survive. The cruise liner, the Diamond Princess, may represent a very interesting and informative case of epidemic analysis. Out of approximately 3,500 cruise passengers, 712 were infected and 10 died, resulting in a mortality rate of 1.4% [6]. However, this should be considered as a high range as it is important to note that these patients were older than the average population and likely suffering from comorbid conditions.

The proliferation of COVID-19 cases was controlled in China, resulting in no reports of new domestic cases as of the 18th of March 2020. High risk patients have been defined as patients above 65 years of age and patients of any age having serious underlying medical conditions, including chronic lung disease, moderate to severe asthma, serious heart conditions, compromised immune systems, severe obesity (body mass index >40), diabetes, and renal failure or liver disease [8]. Currently, at the time of this publication drafting, the outbreak is under control in China, while in Europe and US, the disease has not yet peaked and already 70,459 and 20,601 patients have died, respectively [8]. China has gained experience by treating COVID-19 patients and by conducting clinical trials.

The objective of this manuscript was to identify, report, and analyze registered and published clinical trials and observational studies for the pharmacological treatment of COVID-19 conducted in China. Given that COVID-19 emerged in China and that the Chinese have managed to control the outbreak, with what will likely be a significantly lower number of deaths than in Europe and the United States (US) according to current predictions, supports the importance in gaining insight from these clinical trials and observational studies conducted in China.

2. Method

A strategic search was conducted via the Chinese Clinical Trial Registry and supplemented by searches conducted via the China National Knowledge Infrastructure (CNKI) database, the MEDLINE database, the World Health Organization (WHO) database, and MedRxiv and BioRxiv electronic platforms for preprint articles to identify and extract clinical trials and observational studies conducted in China for the pharmacological treatment of COVID-2019. A primary and secondary descriptive analysis for registered and published clinical studies were performed, respectively. The strategic search of the Chinese Clinical Trial Registry was conducted using the keyword “novel coronavirus” to identify both clinical trials and observational studies registered between January 1st, 2020 and March 25th, 2020. Results from the Chinese Clinical Trial Registry search were included if they met the following inclusion criteria: 1) they were clinical trials or observational studies, 2)the intervention in clinical trials and the exposures in observational studies were pharmacological strategies for the treatment of COVID-19, and 3) they were currently registered in China.

A primary descriptive analysis was performed for registered clinical trials and observational studies identified from Chinese Clinical Trial Registry based on the extraction of the following clinical study information: trial ID, planned date of enrollment, recruitment status, study design, population, sample size, intervention/exposure group, control /reference group, dosage, and primary outcomes. Pharmacological interventions and/or exposures were classified as Western Medicines (WMs), Traditional Chinese Medicines (TCMs), and a combination therapy of WMs and TCMs. WMs were further stratified into antiviral agents, antiparasitic agents, anti-inflammatory agents, biologics, cell-based therapies, plasma therapies, other therapies, and combination therapies of WMs with different mechanisms of action.

The strategic searches of the supplementary databases, CNKI, MEDLINE, WHO, and MedRxiv and BioRxiv platforms, were conducted by employing the following keywords: 1) for the CNKI database: “novel coronavirus”, “2019-nCoV”, “COVID-19” and “SARS-CoV-2”; 2) MEDLINE: “novel coronavirus” AND “clinical studies”, “trials”, “observational studies”; 3) WHO database and preprint platforms with all included paper in pharmacology-related subject area. Results from the supplementary database searches were included if: 1) they met the three inclusion criteria also applied to the Chinese Clinical Trial Registry and 2) if they reported study results. A secondary descriptive analysis was performed for published clinical trials and observational studies identified from supplementary databases based on the following extracted clinical study publication information: study design, population, intervention/exposure group, control /reference group and main results as appropriate. The rationale for the use of WMs reported in the included clinical studies for COVID-19 was reported based on published reviews [9] and electronic reports [10, 11].

No quality assessment was performed. Two researchers independently conducted the searches and extracted information. Any discrepancies identified between the two researchers were reconciled by a third, independent researcher.

3. Results

A total of 221 clinical trials and observational studies for pharmacological treatments of COVID-19 were included from all databases searched. From the Chinese Clinical Trial Registry, 195 registered clinical studies, including 170 clinical trials and 25 observational studies, were identified and included for primary analysis. From the supplementary databases, 26 published clinical studies, including 8 clinical trials and 18 observational studies, were included for secondary analysis. Of these 26 published clinical studies, 18 published clinical studies were identified and included from the CNKI, including 3 clinical trials and 15 observational studies, 2 from MEDLINE, including 1 clinical trial and 1 observational study, from MEDLINE, 2 from WHO, including 1 clinical trial and 1 observational study, and 4 clinical studies, including 3 clinical trials and 1 observational study from MedRxiv and BioRxiv electronic platforms. A total of 43 WMs and 42 TCMs were identified in this study and the rationale for WMs in the treatment of COVID-2019 was summarized in Table 1.

3.1 Primary analysis for registered clinical studies from the Chinese Clinical Trial Registry Results

Of the 482 COVID-19 related studies registered in the Chinese Clinical Trial Registry as of March 21st, 2020, a total of 195 clinical studies, comprising of clinical trials (n=170) and observational studies (n=25), were included from the search. The remaining 287 studies were excluded as 1) they were not clinical trials or observational studies (n=53); 2) they did not investigate the effect of pharmacological treatment (n=189); or 3) they were cancelled by the investigators in the trial registry (n=45). Of the 170 included clinical trials investigating the pharmacological treatment effects of WMs (n=101), TCMs (n=15), and a combination therapy of WMs and TCMs (n=54), the sample size ranged from 10 to 1,000 patients. Of the 25 included observational studies investigating the pharmacological treatment effects of WMs (n=2), TCMs (n=2), and a combination therapy of WMs and TCMs (n=21), the sample size

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ranged from 20 to 2,000 patients. The total number of exposed patients of all the 195 clinical studies included was 24,500.

3.1.1 Clinical trials of pharmacological treatments for COVID-19 in China

Clinical trials of WMs

Of the 101 included trials for WMs, 93 monotherapies were identified, including antivirus agents (n=20), biologics (n=19), antiparasitic agents (n=16), cell-based therapies (n=11), plasma therapies (n=11), anti-inflammatory agents (n=6), other therapies (n=7), and combination therapies of WMs with different mechanisms of action (n=11).

Clinical trials of antivirus agents

Of the 20 included trials for antivirus agents (

Table 2), 14 trials were recruiting as planned, while the remaining 6 trials were pending, most trials (n=12) were randomized clinical trials (RCTs) with sample sizes ranging from 30 to 380 patients. Eleven different antivirus agents were investigated, including Lopinavir-ritonavir(n=6), Favipiravir (n=4), Azvudine (n=4), Danorevir Sodium +Ritonavir (n=3), Baloxavir Marboxil (n=2), ASC09-ritonavir (n=1), Darunavir (n=1), Emtritabine + Tenofovir alafenamide Fumarate (n=1), Triazavirin (n=1), Umifenovir (n=1), and LL-37 antiviral peptide (n=1).

Fifteen of the clinical trials reported 1 primary outcome, while 5 clinical trials reported more than 1 primary outcome. Time to reverse transcription polymerase chain reaction (RT-PCR) negativity (n=7), rate RT-PCR negativity (n=7), rate of composite adverse outcomes (n=4), and time to clinical recovery (n=3) were the most reported primary outcomes (

Table 2).

Clinical trials of biologics

Of the 20 included trials for biologics (Table 3), 11 trials were currently recruiting as planned and most trials (n=17) were RCTs with sample sizes ranging from 30 to 328 patients. Seventeen different biologics were investigated, including Tocilizumab (n=2), Enoxaparin Sodium (n=2), Nebulized Heparin-N-acetylcysteine (n=1), Adalimumab (n=1), Adalimumab +Tocilizumab (n=1), Anti-programmed cell death-1 monoclonal antibody (n=1), Polyinosinic-Polycytidylic Acid (n=1), Probiotics (n=1), Recombinant human granulocyte colony-stimulating factor (n=1), Interferon alpha α1b (n=1), Interferon alpha α1b Eye Drops (n=1), Recombinant Human Interleukin-2 (n=1), Recombinant viral macrophage inflammatory protein (n=1), Regulating intestinal flora (n=1), Thymosin (n=1), Ulinastatin (n=1), Camrelizumab (n=1), and Mycobacterium vaccae injection (n=1).

Eleven of the clinical trials reported 1 primary outcome, while 9 clinical trials reported more than 1 primary outcome. Time to RT-PCR negativity (n=3) and time to clinical recovery (n=3) were the most reported primary outcomes (Table 3)

Clinical trials of antiparasitic agents

Of the 16 included trials for antiparasitic agents (Table 4), 11 trials were currently recruiting as planned and most trials (n=11) were RCTs with sample sizes ranging from 10 to 320 patients. Three antiparasitic agents were investigated, including Chloroquine Phosphate (n=10), Hydroxychloroquine (n=8), and Suramin sodium (n=1).

Eleven of the clinical trials reported 1 primary outcome, while 5 clinical trials reported more than 1 primary outcome. Time to RT-PCR negativity (n=7) and time to clinical recovery (n=5) were the most reported primary outcomes (Table 4).

Clinical trials of cell-based therapies

Of the 11 included trials for cell-based therapies (Table 5), 3 trials were currently recruiting as planned. Most trials (n=8) were RCTs with sample sizes ranging from 16 to 63 patients. Two different cell-based therapies, Mesenchymal stem cells and its exosomes (n=10) and Human natural killer cells-mesenchymal stem cells (n=1), were investigated.

One clinical trial did not report any primary outcomes, 6 clinical trials reported 1 primary outcome, and 4 clinical trials reported more than 1 primary outcome. Chest CT (n=4) and clinical symptoms (n=2) were the most reported primary outcomes (Table 5).

Clinical trials of plasma therapy

Of the 11 included trials for plasma therapies (Table 6), 9 trials were currently recruiting as planned and most trials (n=7) were RCTs with the sample sizes ranging from 10 to 200 patients. Four different plasma therapies were investigated, including Convalescent plasma (n=7), Anti-2019-nCoV virus inactivated plasma (n=3), immunoglobulin of cured patients (n=1), and Umbilical plasma (n=1).

Eight of the clinical trials reported 1 primary outcome, while 3 clinical trials reported more than 1 primary outcome. Clinical symptoms (n=3) and time to clinical improvement (n=2) were the most reported primary outcomes (Table 6).

Clinical trials of anti-inflammatory agents

Of the 6 included trials for anti-inflammatory agents (Table 7), 4 trials were currently recruiting as planned and most trials (n=5) were RCTs with sample sizes ranging from 16 to 200 patients. Five different anti-inflammatory agents were investigated, including Methylprednisolone (n=2), Corticosteroid (n=1), Jakotinib hydrochloride (n=1), Leflunomide (n=1), and Tranilast (n=1).

Four of the clinical trials reported 1 primary outcome, while 2 clinical trials reported more than 1 primary outcome. Time RT-PCR negativity (n=2) was the most reported primary outcome (Table 7).

Clinical trials of other WMs

Of the 6 included trials for other WMs (Table 8), 4 trials were currently recruiting as planned (n=4) and most trials (n=5) were RCTs with sample sizes ranging from 40 to 520 patients. Five drugs were investigated, including Pirfenidone (n=2), Hydrogen Peroxide gargle (n=1), Lipoic acid injection (n=1), Bismuth potassium citrate (n=1), and Carrimycin (n=1).

All of the clinical trials (n=6) reported 1 primary outcome. The rate of RT-PCR negativity (n=3) was the most reported primary outcome (Table 8).

Clinical trials of WM combination therapies

Of the 11 included trials for WM combination therapies (Table 9), 10 trials were currently recruiting as planned and most trials (n=9) were RCTs with sample sizes ranging from 30 to 150 patients. Nine trials investigated the effects of antivirus agents combined with biologics (n=7), an antiparasitic agent (n=1) or a biologic plus anti-inflammatory agent (n=1), while 2 trials investigated 2 cell-based therapies combined with a biologic (n=1) or an anti-inflammatory agent (n=1).

Eight of the clinical trials reported 1 primary outcome, while 3 clinical trials reported more than 1 primary outcome. Chest CT (n=4) was the most reported primary outcome (Table 9).

Clinical trials of TCMs

Of the 15 included trials for TCMs, 9 trials reported the specific names of investigated TCMs. Of these 9 trials, specifying TCMs (Table 10), 4 trials were currently recruiting as planned and most trials (n=6) were RCTs with sample sizes ranging from 60 to 400 patients. Thirteen different TCM compounds were investigated in these 9 trials specifying TCMs.

Five of the clinical trials reported 1 primary outcome, while 4 clinical trials reported more than 1 primary outcome. Clinical symptoms (n=3) was the most reported primary outcome (Table 10).

Clinical trials of WM and TCM combination therapies

Of the 54 included trials for WM and TCM combination therapies, 31 trials reported the specific names of investigated TCMs. Of the 31 trials specifying TCMs combined with WMs (

Table 11), 21 trials were currently recruiting as planned and most trials (n=26) were RCTs with sample sizes ranging from 20 to 408 patients. Thirty-six different TCM compounds were combined with standard of care (SOC) (n=33), lopinavir-ritonavir(n=10), lopinavir-ritonavir + Interferon α2b (n=1), and Umifenovir (n=1) in these 31 trials specifying TCMs.

Twenty-one of the clinical trials reported 1 primary outcome, while 10 clinical trials reported more than 1 primary outcome. Chest CT (n=8), time to clinical recovery (n=7), and clinical symptoms (n=7) were the most reported primary outcomes (Table 11).

3.1.2 Observational studies of pharmacological treatments for COVID-19 in China

Of the 25 included observational studies for pharmacological treatments, 6 studies reported the specific names of investigated interventions, while the others (n=19) did not. Two WMs, including antivirus agents plus biologics (n=1) and a cell-based therapy (n=1) were investigated, while 3 TCMs, including Qing-Fei detoxification (n=2), Triple energizer (n=1), and Xin-Guan-1 formula (n=1) were investigated. Of the 6 observational studies specifying interventions (

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Table 12), 4 studies were currently recruiting as planned and 1 study was completed. Half of the studies (n=3) were cohort studies with sample sizes ranging from 100 to 237 patients and the other half of studies (n=3) were case series with sample sizes ranging from 20 to 100 patients.

Two of the observational studies reported 1 primary outcome, while 4 observational studies reported more than 1 primary outcome. Chest CT (n=2) and blood routine tests (n=2) were the most reported primary outcomes (

Table 12).

3.2 Secondary analysis for published clinical studies from supplementary databases: CNKI, MEDLINE, WHO, and MedRxiv and BioRxiv Platforms

From the supplementary searches of the CNKI, MEDLINE, WHO, and MedRxiv and BioRxiv platforms, a total of 27 published clinical studies, including 8 clinical trials and 19 observational studies were included for secondary analysis. Of the 8 clinical trials, 3 were identified and included from CNKI [12-14], 1 from MEDLINE [15], 1 from WHO [16], and 3 from the MedRxiv and BioRxiv platforms [17-19]. Of the 18 observational studies, 15 were identified and included from CNKI [20-34], 1 from MEDLINE [35], 1 WHO database [36], and 1 was from MedRxiv electronic platform [37].

3.2.1 Published clinical trials from supplementary searches

Of the 8 included trials (Table 13), all trials were RCTs with sample size ranging from 30 to 240 patients; and 7 different interventions were investigated, including 5 WMs and 2 TCMs combined with WMs. Treatment with Lopinavir-ritonavir (n=99) was not associated with a difference from SOC (n=100) in the time to clinical improvement ($p>0.05$) and mortality at 28 days (19.2% vs. 25.0%, $p>0.05$). Treatment with Lopinavir-ritonavir (n=21) or Umifenovir (n=16) was not associated with a difference from SOC with no antiviral drugs (n=7) in time of positive-to-negative conversion of SARS-CoV-2 nucleic acid, the rates of antipyresis, cough alleviation, improvement of chest CT or the deterioration rate of clinical status (all $P > 0.05$). Treatment with Ribavirin + Lopinavir-ritonavir + Interferon α (n=21) was not associated with a difference from Lopinavir-ritonavir + Interferon α (n=46) in time to RT-PCR negativity and days of hospitalization; treatment with Favipiravir + SOC (n=116) was associated with a difference from Umifenovir + SOC (n=120) in clinical recovery rate of day 7 (71.43% vs 55.86%, $P=0.0199$), fever reduction and cough relief ($P<0.001$); More adverse events (13.79% vs 2.50%, $P<0.0001$); treatment with Hydroxychloroquine (n=15) was not associated with a difference from SOC (n=15) in rate of RT-PCR negativity (86.9% vs. 93.3%. $p>0.05$); treatment with Hydroxychloroquine + SOC (n=31) was associated with a difference from SOC (n=31) in time to clinical recovery and proportion of patients with improved pneumonia (80.6% vs 54.8%); treatment with Lopinavir-ritonavir+ interferon α + Lian-Hua-Qing-Wen capsule (n=30) was found to significantly improve effective rate of treatment (76.7% vs. 46.7%, $p<0.01$) compared with Interferon α + Lian-Hua-Qing-Wen capsule (n=30) ; and treatment with Tou-Jie-Qu-Wen Granule + Umifenovir (n=20) was found to significantly improve the TCM syndrome score, absolute value of lymphocyte and value of C reactive protein compared with Umifenovir alone (n=17) (Table 13).

3.2.2 Published observational studies from supplementary searches

Of the 18 included observational studies (Table 14), most studies (n=14) reported the specific name of all investigated interventions in the publications, while the others (n=4) did not report the name of investigated TCMs. Most of the studies (n=12) were retrospective case series with sample sizes ranging from 10 to 463 patients, while the remaining studies (n=6) were retrospective cohort studies with sample sizes ranging from 28 to 134 patients. Twelve different interventions were investigated including 10 WMs and 3 TCMs. Treatment with Lopinavir-ritonavir + Interferon α + Symptom treatment (n=52) and Umifenovir + Interferon α + Symptom treatment (n=34) were not associated with a difference from Interferon α + Symptom treatment (n=48) in rate of RT-PCR negativity (71.8% vs. 82.6% vs. 77.1%, $P= 0.79$) and a difference in number of patients still in progress (22 vs 13 vs 25, $P=0.3$). Treatment with Umifenovir + Lopinavir-ritonavir (n=16) was associated with a difference from Lopinavir-ritonavir (n=17) in the rate of RT-PCR negativity (75% vs 35%, $P<0.05$) and chest CT (69% vs 29%, $P<0.05$); treatment with Meplazumab + SOC (n=17) was associated with a difference from SOC (n=11) in the discharged ($p=0.006$) and case severity ($p=0.021$) in critical and severe patients; and

treatment with Shu-Feng-Jie-Du Capsule (n=35) was found to significantly improve the symptoms and time to RT-PCR negativity ($p<0.05$) compared with Umifenovir alone (n=35) (Table 14).

4. Discussion

A total of 195 clinical studies, comprising of clinical trials (n=170) and observational studies (n=25), were included from the Chinese Clinical Trial Registry. Altogether, 24,500 patients were planned to be exposed in these clinical studies. Among the 170 clinical trials involving 17,151 patients, 101 tested WMs, 15 tested TCMs, and 54 tested a combination of TCMs and WMs. 129 of these were RCTs. Currently, 113 clinical trials were still recruiting, however, it is expected that most studies have finished their enrollment because they have at least run for more than one month and may not take more than three weeks to finalize the enrollment during the period of COVID-19 pandemic outbreak.

The numbers of registered clinical studies and exposed patients in China are very impressive and suggest a massive knowledge has been acquired from China as what is presented in this paper is only clinical experience and does not include the critical experience of radiologists and virology laboratories.

TCMs remain of high interest within the Chinese medical community and despite WMs being studied as well, there is still a significant place for TCMs. However, there were still more WMs and combination therapies of WMs and TCMs being studied than TCMs.

The rationale for testing a specific product or a combination of products is not always provided in clinical trials and observational studies. However, several rationales for the investigation of WMs may be considered in the case of this outbreak, such as interventions that have been shown to be effective with other coronaviruses, SARS-COV-2 in vitro, and other viruses as well as interventions that may control the cytokine release, that are based on Mesenchymal stem cells therapies, and interventions with antibodies from patients already recovered from the disease. In relation to TCMs, one of the main concepts of TCM theory is the balance of Yin and Yang, which have been utilized as interventions against COVID-19 to enhance immune defense, relieve fever, restore biological and physiological imbalance, inhibit virus and bacteria, and reduce the inflammatory response of the body caused by the virus and bacteria in mild and moderate patients as well as to gain time and ultimately rescued patients in sever conditions [38]. TCMs were considered not only as adjuvant therapies but also as curative therapies in the COVID-19 outbreak in China and recommended by Chinese clinical guidelines for COVID-19 issued by the National Health Commission of the People's Republic of China [39].

The gold standard of a clinical trial study design is the double-blinded RCT. The process of developing a golden standard clinical trial is unlikely to be feasible within the context of a pandemic outbreak, due to the several months it usually requires to secure pharmaceutical development quality control testing. Therefore, it may be understandable that the studies conducted were not double blinded. As the majority of trials were randomized, this may still guarantee a high likelihood of comparability between treatment arms of the clinical trials. The comparator in gold standard RCTs is always SOC. It is unclear if SOC has been standardized to be comparable in the trials identified and included in this paper. However, in the context of a pandemic outbreak, specifically COVID-19, the SOC would be to ensure vital functions were maintained, especially respiratory functions. Therefore, SOC among the trials identified and included would likely be very similar, especially due to the vast amount of published guidelines in China for the medical management of COVID-19, specifically in relation to the maintenance of respiratory functions.

It will be important to ensure that concomitant therapies, such as biotherapies, corticosteroids, and non-steroid anti-inflammatory drugs, among others, are proportionally used in comparative arms to

a reasonable degree. However, it is important that biological, viral analysis, and thoracic imaging are blinded.

In the case of a pandemic outbreaks, such as COVID-19, tensions arise in healthcare systems and strain is placed on the availability of human resources, material resources, and pharmaceuticals. Due to pharmaceutical scarcity, it is possible that clinical trial procedures may not have been fully respected, therefore, potentially introducing biases. However, as several trials were performed for each intervention, a meta-analysis could be performed and may provide robust outcomes integrating the variability of these trials and estimating the effect size of these interventions.

The large number of trials currently registered in China and still open to recruitment, has led to the relative paucity of publications of study results. However, the international scientific community has been eager for the scientific communication and exchange of the large knowledge accumulated in China on the treatment of COVID-19.

It is surprising that WHO has not acted to ensure the expedited dissemination of the continuously accumulating knowledge in China. There is no public evidence of any third party advocating to Chinese authorities to publicly share the vast knowledge accumulated in China.

Other challenges while performing clinical trials for this particular condition is that a large number of patients of patients are asymptomatic and may recover without being aware of their infection statues and, ultimately, without treatment. For mild and moderate patients, SOC followed the guidance of the “Diagnosis and Treatment Protocol for COVID-19 Pneumonia” published by the Chinese National Health Commission [39] has proven to be effective.

Therefore, additional pharmacological treatments other than SOC should be targeted towards to high-risk or very high-risk patients who will eventually end up in intensive care. Treating patients too early may result in a significant number of spontaneously resolved cases, which would require large clinical trial sample sizes to derive conclusions. Treating patients too late may result in the treatment of patients for which the virus is likely cleared, or the inflammatory lesions and bacterial infection as consequences of being infected with the virus will be life threatening. Defining the optimal patient populations and time of enrollment for a COVID-19 trial may be as important as the treatment’s effectiveness. Analysis of patient subgroups based on different criteria, including virologic load and further investigation of infection severity level of included patients in clinical trial data may be informative to address these issues.

A great deal of attention has been brought to the possible benefits of chloroquine and derivatives, the broadly used antimalarial drugs. Researchers from the Wuhan Institute of Virology [40] evaluated in vitro 5 FDA-approved drugs and 2 broad spectrum antivirals against a clinical isolate of SARS-CoV-2 and concluded that "chloroquine is highly effective in the control of 2019-nCoV infection in vitro" and that its "safety track record suggests that it should be assessed in human patients suffering from the novel coronavirus disease.” Researchers from Wuhan University published a report on the use of hydroxychloroquine and found that, among 80 systematic lupus erythematosus patients treated with hydroxychloroquine, none of them were infected with SARS-CoV-2 during the outbreak.

More recently, researchers from the Shanghai University attributed the ability to control the outbreak of COVID-19 in their hospital to the systematic introduction of chloroquine and hydroxychloroquine beginning on February 5th, 2019. Researchers from the Qingdao University indicated that "according to the news briefing, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course." In

France, a clinical study in Marseille [41] reported a 100% viral clearance in nasopharyngeal swabs in 6 patients after 5 and 6 days of the combination of hydroxychloroquine and azithromycin. The French Ministry of Health recently allowed the use of hydroxychloroquine to treat COVID-19 disease pending the results of ongoing clinical trials. However, an observational study in Paris [42] reported that repeated nasopharyngeal swabs in 10 patients using a RC-PCR assay were still positive for SARS-CoV2 RNA in 8/10 patients at days 5 to 6 after treatment initiation. Within 5 days, one patient died, two were transferred to the ICU, and one patient discontinued because of cardiotoxicity. In the absence of virologic or clinical benefit of chloroquine in a number of viral infections, the option of using chloroquine in the treatment of SARS-CoV-2 should be examined with attention in light of the recent promising announcements. Two new observational studies from Marseille support the use of hydroxychloroquine in association with Azithromycin [41, 43]. The last one [43] gather data among 1, 061 treated patients they observed 98% cure, 4% of hospitalisation including 1% in ICU and 0.5% death. Current death rate in 3.5% globally and the lowest one in Germany and Korea is 2%.

In Chinese governmental treatment guideline for COVID-19 [44], chloroquine and hydroxychloroquine appeared as the pillar therapy for COVID-19. It remains unfortunate that more knowledge has not been shared about the selection rationale and associated outcome of using hydroxychloroquine at this point on time of the pandemic may severely target Africa. In Africa, the healthcare infrastructure is totally unable to absorb the consequences of a pandemic that will affect up to one-third or more of the population. The experience-based treatment guidelines may not be enough and more evidence must be generated to facilitate the dissemination of not only clinical experience, but also the scientific evidence from China and their ability to overcome the outbreak to the rest of the world.

Physical distancing is unlikely feasible in Africa due to cultural standards and extreme poverty. People currently live with immediate and extended families in a single room housing up to 20 people or more. In large cities and large city suburbs, rooms with several large families are built one next to other with no clear separation of property. It is also common cultural practice and courtesy that when someone falls ill, all the relatives and close friends visit with the ill to check on them and spend time. Most people in Africa are living off of informal work and are paid daily as it is non-contractual. These daily wages feed their large families and they will face the decision as to whether they will respect confinement measures put in place, risking the loss of their daily salary, and, ultimately, being unable to feed their families, or they will leave confinement to work and as a byproduct disseminate the coronavirus. To battle COVID-19, they have been recommended to wash their hands repeatedly while a vast majority do not have access to water and if they do, they must carry it by hand across long distances. Moreover, they have little access to soap. They are recommended to blow their nose in disposable handkerchiefs, which may not even be affordable. They are recommended to sneeze in their elbows while they mostly dress short sleeves during the hot summer season.

Obviously without an effective pharmaceutical that is affordable like hydroxychloroquine or chloroquine a disaster is brewing in Africa and other countries, such as India. The lack of WHO clear recommendations for using the ammunition considered by Chinese as one of the ultimate options to control pandemic may have long term consequence on WHO's credibility in developing countries. Instead WHO continues to provide inapplicable guidance and warns against the use of chloroquine. WHO's credibility has been questioned during the Ebola, Zika, and Chikungunya outbreaks [45].

5. Conclusion

China is generating a massive source of evidence that is critical for defeating the COVID-19 pandemic. The authors encourage Chinese scientists to share this knowledge. The knowledge about TCMs is likely difficult to transfer in a short time for an outbreak. It deserves further analysis. Among all tested pharmacological agents, evidence and guidelines in China points toward hydroxychloroquine and

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chloroquine being the effective therapies, but this observation is mainly based on the clinical experience and limited published studies. However, evidence has accumulated ex-China to support the benefit of hydroxychloroquine in the treatment of COVID-19. More evidence is under generation and should be shared with the global scientific community.

References

1. Lai, C.C., et al., *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges.* Int J Antimicrob Agents, 2020. **55**(3): p. 105924.
2. Huaxia, *New-type coronavirus causes pneumonia in Wuhan: expert*, in *XINHUANET News Report.*
3. *World Health Organization (WHO)*. Available from: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic.
4. Lu, H., C.W. Stratton, and Y.W. Tang, *Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle.* J Med Virol, 2020. 92(4): p. 401-402.
5. Emma Farge, S.N., *United States could become coronavirus epicenter: WHO*, in *GENEVA (Reuters)*. 2020
6. *Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)* 2020 [cited 2020 March 26]; Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
7. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---3-march-2020, W.H.O.A.f.
8. *Number of coronavirus (COVID-19) deaths in Europe since February 2020 (as of March 28, 2020), by country and date of report*. 2020 [cited 2020 March 29]; Available from: https://www.statista.com/statistics/1102288/coronavirus-deaths-development-europe/.
9. Wang, L.-s., et al., *A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence.* International Journal of Antimicrobial Agents, 2020: p. 105948.
10. Jeffrey K Aronson, R.E.F., Nicholas DeVito, Carl Heneghan, *COVID-19 trials registered up to 8 March 2020—an analysis of 382 studies*. 2020
11. McGrath, J., *All the COVID-19 vaccines and treatments currently in clinical trials*. 2020
12. FU Xiaoxia, L.L., TAN Xinghua, *Clinical study on 37 case of COVID-19 treated with integrated traditional Chinese and Western Medicine.* Traditional Chinese Drug Research and Clinical Pharmacology, (1003-9783,CN 44-1308/R).
13. Xue-mei, W.S.-z.W.H.-j.C.H.-m.Y.Y.B.F.-j.Z., *Lianhua Qingwen capsule and interferon-α combined with lopinavir /ritonavir for the treatment of 30 COVID-19 patients.* J Bengbu Med Coll, 2020. February 2020,Vol.45,No.2.
14. CHEN Jun, L.D., LIU Li, LIU Ping, XU Qingnian, XIA Lu, LING Yun, HUANG Dan, SONG Shuli, ZHANG Dandan, QIAN Zhiping, LI Tao, SHEN Yinzhong, LU Hongzhou, *A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19).* JOURNAL OF ZHEJIANG UNIVERSITY, 2020
15. Cao, B., et al., *A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.* N Engl J Med, 2020.
16. Yuan, J., et al., *The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients.* Inflamm Res, 2020.
17. Chen, Z., et al., *Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial.* medRxiv, 2020: p. 2020.03.22.20040758.
18. Li, Y., et al., *An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI).* medRxiv, 2020: p. 2020.03.19.20038984.
19. Chen, C., et al., *Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial.* medRxiv, 2020: p. 2020.03.17.20037432.
20. SHI Jia, Y.Z., Ye Chen et *Clinical observation on 49 cases of non-critical cornavirus disease 2019 in Shanghai treated by intergrated traditional Chinese and western medicine.* Shanghai Journal of Traditional Chinese Medicine, 2020.

21. Xia Wenchang, A.C., Zheng Chanjuan, *34 Cases of New Coronavirus Pneumonia treated with Integrated Traditional Chinese and Western Medicine.* Journal of Traditional Chinese Medicine, 2020.
22. QU Xiang-kun, H.S.-l., MA Jing-he, WEI Guang-you, SONG Ke-yi, TANG Chao, GAO You-fang, LIANG Shao-qin, DU Wen-jie, *Observation on clinical effect of Shufeng Jiedu Capsule combined with Arbidol Hydrochloride Capsule in treatment of COVID-19.* Chinese Traditional and Herbal Drugs 2020.
23. CHEN Jun, L.y., Xl xiu hong, *The treatment effectiveness of Lopinaviltonivir and Abidol for Coronavirus disease.* Chinese Journal of Infectious Diseases, 2020.
24. CHENG Dezhong, L.Y., *Clinical Effectiveness and Case Analysis in 54 NCP Patients Treated with Lanhuaqingwen Granules.* World Chinese Medicine, January . 2020, . **Vol.15,No.2**.
25. Lu, R., W. Wang and X. Li., *Clinical observation on 63 cases of suspected cases of new coronavirus pneumonia treated by Chinese medicine Lianhua Qingwen.* Tradit. Chin. Med., 2020.
26. Yao, K., M. Liu, X. Li, J. Huang and H. Cai., *Retrospective clinical analysis on treatment of novel coronavirus-infected pneumonia with traditional Chinese medicine Lianhua Qingwen.* Chin. J. Exp. Tradit. Med. Formulae,, 2020
27. Medicine, N.A.o.T.C., *Beijing's first confirmed case of new coronavirus pneumonia cured by Symptomatic and Chinese medicine treatment National Administration of Traditional Chinese Medicine, Beijing, 2020.* 2020.
28. Administration, G.M.P., *Notice on the clinical use of Tongjie Quwen Granules (formerly known as "pneumonia No. 1")*. 2020.
29. Yu Simiao, W.Z., Qin Enqiang, *Clinical characteristics 25 patients with novel coronavirus pneumonia.* Chinese Journal of Integrated Traditional Chinese and Western Medicine, 2020.
30. XU Kaijin, C.H., SHEN Yihong et., *Management of corona virus disease-19 (COVID-19): the Zhejiang experience.* Journal of Zhejiang University(Medical Sciences), 2020.
31. Zhu Miao, L.Q., Gu Minghua et., *Clinical diagnosis and intergrated treatment of traditional Chinese medicine and western medicine for confirmed patients with cornavirus disease 2019 in Yangzhou city of Jiangsu province* Journal of Clinical Medicine in Practice, 2020.
32. GAO Ting, X.Y., HE Xiaopeng et, *Epidemiological and clinical characteristics of 40 patients with coronavirus disease 2019 outside Hubei.* Chinese Journal of Respiratory and Critical Care Medicine, 2020.
33. Weining, Z.X.Z.D.Z.J.e., *Clinical characteristics of 463 patients with common and severe type coronavirus disease 2019.* Shanghai Medical Journal, 2020.
34. LI Weijie, W.L., XU Yanjiao, GUO Jieru, ZHANG Chengliang, LIU Dong, LI Juan, *Drug Utilization Evaluation on Antiviral Treatment in Patients with Severe Coronavirus Disease 2019: Lopinavir/ritonavir.* Herald of Medicine, 2020.
35. Duan, K., et al., *Effectiveness of convalescent plasma therapy in severe COVID-19 patients.* Proc Natl Acad Sci U S A, 2020.
36. Deng, L., et al., *Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study.* J Infect, 2020.
37. Bian, H., et al., *Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial.* medRxiv, 2020: p. 2020.03.21.20040691.
38. Ren, J.L., A.H. Zhang, and X.J. Wang, *Traditional Chinese medicine for COVID-19 treatment.* Pharmacol Res, 2020. 155: p. 104743.
39. *National Health Commission & State Administration of Traditional Chinese Medicine, Diagnosis and Treatment Protocol for COVID-19 Pneumonia*. 2020.
40. Wang, M., et al., *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.* Cell Research, 2020. 30(3): p. 269-271.

41. Gautret, P., et al., *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.* International Journal of Antimicrobial Agents, 2020: p. 105949.
42. Molina, J.M., et al., No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection, Med Mal Infect, 2020.
43. Raoult Didier, Available from: https://www.mediterranee-infection.com/wp-content/uploads/2020/04/Abstract_Raoult_EarlyTrtCovid19_09042020_vD1v.pdf, 2020.
44. Province, H.C.o.G., *Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia.* Chinese Journal of Tuberculosis and Respiratory Diseases, 2020. **43**(3): p. 185-188.
45. PATTERSON, A.S., *Here's why the WHO responded so differently to Zika and Ebola*. 2016, Washington post.

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Tables and figures

Table 1 Rationale for the use of WMs for COVID-19

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Drug name	Description	Mechanism of Action	Rationale for managing COVID-2019
Anti-virus agents			
Lopinavir-ritonavir	HIV protease inhibitor	Bind to the key enzyme for coronavirus replication and suppress coronavirus activity	In vitro, animal model and possible clinical efficacy
Favipiravir	Broad spectrum inhibitor of RNA-dependent RNA polymerase, typically used in treating influenza	Inhibit viral RNA synthesis	In vitro and possible clinical efficacy
Azvudine	Azidocytidine nucleoside analogue and HIV reverse transcriptase inhibitor	Prevent virus from replicating	Possible clinical efficacy
Danorevir Sodium + Ritonavir	Peptidomimetic inhibitor of the NS3/4A protease of HCV	Structure similarity between chymotrypsin-like protease of SARS-CoV-2 shares and HCV proteases	Possible clinical efficacy
Baloxavir Marboxil	Inhibitor of influenza virus cap-dependent endonuclease	Similarities between SARS-CoV-2 and H5N1	Possible clinical efficacy
ASC09-ritonavir	HIV protease inhibitor	Structure similarity between chymotrypsin-like protease of SARS-CoV-2 shares and HIV proteases	Possible clinical efficacy
Darunavir	HIV protease inhibitor	Structure similarity between chymotrypsin-like protease of SARS-CoV-2 shares and HIV proteases	Possible clinical efficacy
Emtritabine + Tenofovir alafenamide Fumarate	HIV reverse transcriptase inhibitor	Prevent virus from replicating	Possible clinical efficacy
Triazavirin	Broad spectrum non-nucleoside antiviral drug with efficacy against influenza A and B	Similarities between SARS-CoV-2 and H5N1	Possible clinical efficacy
Umifenovir	Broad spectrum inhibitor of membrane haemagglutinin fusion,typicaly in influenza viruses	Reduce the risk of bacterial pneumonia	Possible clinical efficacy
Biologics			
Interferon	Activate cytoplasmic enzymes affecting viral messenger RNA translation and protein synthesis	Crucial cytokines in immune system	Possible clinical efficacy
Enoxaparin and Nebulized Heparin-N-acetylcysteine	Anti-clotting agent, know as low molecular weight heparin	Heparin as a potential attachment factor for the Spike Protein of SARS-CoV-2 virus	In vitro and possible clinical efficacy
Tocilizumab	IL-6 Receptor-Inhibiting Monoclonal Antibody	Inhibit diverse physiological processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute-phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation	Possible clinical efficacy
Adalimumab	Targeting TNF-alfa	Used to treat rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis, and uveitis	Possible clinical efficacy
Anti-programmed cell death-1	Targeting receptors for PD-1	Limit T cell activity during infection to reduce inflammation	Possible clinical efficacy
Polyinosinic-Polycytidylic Acid	Toll like receptor agonists (TLR)3	Augment the production of IFN-α, -β, and -γ, which consequently inhibited CoV replication and compensated for the inhibitory effectsof CoV on IFN signaling pathways	In vitro and possible clinical efficacy
Probiotics and intestinal flora regulator	Interact with gut microbiome to reinforce our immune system	Elevating immunogenicity by influencing seroconversion and seroprotection rates	Possible clinical efficacy
Recombinant human granulocyte colony-stimulating factor,rhG-CSF	Directs the activation, proliferation, and differentiation of myeloid-derived cells and causes maturation of antigen-presenting cells, thus affecting adaptive immune responses	3C-like protease of SARS-CoV-1 reduces expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) in transfected cells	In vitro and possible clinical efficacy
Recombinant Human Interleukin-2	Multiple anti-inflammatory actions	Crucial cytokines in immune system	Possible clinical efficacy
Recombinant viral macrophage inflammatory protein	Advanced Therapy Medicinal Products	Not known	Possible clinical efficacy

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Thymosin	A group of polypeptides, initially isolated from the thymus	Involved in T-cell differentiation and used in cancer treatment with little evidence of benefit	Possible clinical efficacy
Ulinastatin	Protease inhibitor to inhibit the activity of polymorphonuclear leukocyte elastase	Modulating inflammatory reaction	Possible clinical efficacy
Camrelizumab	Anti-PD-1 checkpoint inhibitor and used in China to treat Hodgkin's lymphoma and nasopharyngeal carcinoma	Being compared to thymosin for the prevention of sepsis in COVID-19 patients	Possible clinical efficacy
Maplazumab	Targeting CD147	Not known	Possible clinical efficacy
Mycobacterium vaccae injection	The same genus as Mycobacterium tuberculosis	Not known	Possible clinical efficacy
Antiparasitic agents			
Chloroquine and Hydroxychloroquine	Antimalarial actions and some efficacy in HIV-AIDS	Inhibit glycosylation of viral ACE-2 or inhibition of quinone reductase 2, reducing synthesis of viral sialic acid	In vitro and possible clinical efficacy
Suramin sodium	Used to treat first-stage African trypanosomiasis and onchocerciasis	Not known	Possible clinical efficacy
Cell-based therapy			
Mesenchymal stem cells	Adult stem cells and can be taken from either humans or animals	Efficacy of treating lung damage caused by radiation for cancer treatment	Possible clinical efficacy
Plasma therapy			
Convalescent plasma	Contains nonspecific antibodies	Block viral Fc receptor activation by boosting endogenous neutralizing antibodies and preventing antibody-dependent enhancement of infection	Possible clinical efficacy
Anti-inflammatory agents			
Methylprednisolone and Corticosteroid	Anti-inflammatory actions	Experience with corticosteroids in other infectious diseases has not been uniformly beneficial and in SARS corticosteroids may worsen the disease	Possible clinical efficacy
Jakotinib hydrochloride	Chinese literature only and presumed inhibitor of Janus-associated kinases	Not known	Possible clinical efficacy
Leflunomide	Immunosuppressant and inhibitor of dihydro-orotate dehydrogenase and tyrosine kinases	Causes degradation of intracellular transcription factors and used to treat rheumatoid arthritis and psoriatic arthritis	Possible clinical efficacy
Tranilast	Anti-allergic and inhibitor of NLRP3 in the inflammasome pathway	Modulating inflammatory reaction	Possible clinical efficacy
Others			
Pirfenidone	Reduces fibroblast proliferation and production of fibrosis-associated proteins and cytokines	Not known	Possible clinical efficacy
Hydrogen Peroxide gargle	Non-specific supposed antiviral action in the throat	Not known	Possible clinical efficacy
Lipoic acid injection	Vitamin-like antioxidant	Not known	Possible clinical efficacy
Bismuth potassium citrate	Inhibits growth of Helicobacter pylori	May inhibit SARS-CoV1 helicase	In vitro and possible clinical efficacy
Carrimycin	Polyether antibiotic and active against Gram-positive bacteria, mycoplasma, fungi and yeasts	Not known	Possible clinical efficacy

HIV: The human immunodeficiency viruses; RNA: Ribonucleic acid; HCV: Hepatitis C; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; H5N1: A bird-adapted strain of H5N1; IL-6: Interleukin-6; TNF: Tumor necrosis factor; PD-1: programmed cell death protein 1; GM-CSF: granulocyte-macrophage colony-stimulating factor; INF: Interferons; ACE: Angiotensin-converting enzyme; HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome

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Table 2 Clinical trials of antivirus agents for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000029548	04/02/2020	Pending	Non-RCT	COVID-19 pneumonia (n=30)	Group 1: Baloxavir Marboxil (80mg on day1,80mg on day4, 80mg on day7 as necessary); Group 2: Favipiravir (First dose: 1600mg; then 600mg, tid for no more than 14 days) Group 3: Lopinavir-ritonavir (200mg/50 mg, bid for 14 days)	NA	Time to nucleic acid negativity; Time to clinical improvement
ChiCTR2000029541	10/02/2020	Pending	RCT	COVID-19 pneumonia (n=120)	Group 1: Darunavir-cobicistat (800mg/150mg, qd) + Thymosin α1 (1.6 mg, sc, qod) + Standard of care; Group 2: Lopinavir-ritonavir (400mg/100mg, bid) + Thymosin α1 (1.6mg+ sc,qod) + Standard of care	Thymosin a1 (1.6 mg, sc, qd) + Standard of care	Time to nucleic acid negativity
ChiCTR2000030187	25/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=60)	Lopinavir-ritonavir	Standard of care	Mortality; Rate of nucleic acid negativity
ChiCTR2000029308	10/01/2020	Recruiting	RCT	COVID-19 pneumonia (n=160)	Lopinavir-ritonavir (400mg/100mg, bid)	Standard of care	Time to clinical improvement
ChiCTR2000029539	04/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=328)	Lopinavir-ritonavir+ Standard of care Standard of care	Standard of care	Rate of composite adverse outcome
ChiCTR2000029996	20/02/2020	Recruiting	RCT	Moderate COVID-19 pneumonia (n=60)	Group1: Farpiravir (First dose 1600mg; then 200mg bid for 9 days); Group 2: Farpiravir (First dose 1800mg; then 200mg bid for 9 days); Group 3: Farpiravir (First dose 2400mg; then 200mg bid for 9 days)	NA	Time to clinical recovery
ChiCTR2000029544	04/02/2020	Pending	RCT	COVID-19 pneumonia (n=30)	Group 1: Baloxavir Marboxi + Standard of care; Group 2: Fabiravir + Standard of care	Standard of care	Time to and rate of nucleic acid negativity; Time to clinical improvement
ChiCTR2000030041	25/02/2020	Pending	Non-RCT	Moderate and severe COVID-19 pneumonia (n=40)	Azivudine	NA	Rate of nucleic acid negative
ChiCTR2000029853	16/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=20)	Azivudine (5 tablets, qd)	Standard treatment	Time to clinical recovery; Time to and rate of nucleic acid negativity; Blood routine test; Rate of progression; Days of hospitalization; Mortality
ChiCTR2000030487	04/03/2020	Recruiting	Non-RCT	Moderate and severe COVID-19 pneumonia (n=10)	Azivudine (10 mg, qd on the first day; then 5 mg, qd) + Standard of care	NA	Time to and rate of nucleic acid negativity
ChiCTR2000030424	02/03/2020	Pending	Non-RCT	Moderate and severe COVID-19 pneumonia (n=30)	Azivudine (10 mg, qd on the first day; then 5 mg, qd) + Standard of care	NA	Time to and rate of nucleic acid negativity

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Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000030000	16/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=40)	Group 1: Danoprevir Sodium + Ritonavir Group 2: Pegasys injection Group 3: Novaferon Group 4: Lopinavir-ritonavir	TCM + Spray inhalation	Rate of composite adverse outcomes
ChiCTR2000030259	22/02/2020	Recruiting	RCT	Mild and Moderate COVID-19 pneumonia (n=60)	Danoprevir Sodium + Ritonavir	Standard of care	Rate of composite adverse outcomes
ChiCTR2000030472	25/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=20)	Danoprevir Sodium + Ritonavir + Standard of care	Standard of care	Rate of composite adverse outcomes
ChiCTR2000030113	22/02/2020	Recruiting	RCT	COVID-19 pneumonia with poorly responsive Lopinavir/ritonavir (n=30)	Favipiravir	Lopinavir-ritonavir	Blood routine tests, Chest CT
ChiCTR2000029603	06/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=160)	ASC09-ritonavir+ Standard of care	Lopinavir-ritonavir + Standard of care	Rate of composite adverse outcomes
ChiCTR2000029468	01/02/2020	Pending	Non-RCT	COVID-19 pneumonia (n=120)	Emtritabine + Lopinavir-ritonavir + Tenofovir alafenamide Fumarate	Lopinavir-ritonavir	Survival rate
ChiCTR2000030001	15/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=240)	Triazavirin + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000029621	07/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=380)	Umifenovir + Standard of care	Standard of care	Rate of nucleic acid negativity
ChiCTR2000030939	16/03/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=10)	LL-37 antiviral peptide	NA	Time to and rate of nucleic acid negativity

The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; qd: Once a day; bid: twice daily; tid: three times a day; qod: every other day; sc: subcutaneous; CT: computed tomography

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Table 3 Clinical trials of biologics for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000029765	10/02/2020	Recruiting	RCT	Moderate and severe COVID-19 pneumonia (n=188)	Tocilizumab + Standard of care	Standard of care	Clinical cure rate
ChiCTR2000030196	20/02/2020	Pending	Non-RCT	Moderate and severe COVID-19 pneumonia (n=60)	Tocilizumab + Standard of care	NA	The relive of cytokine release syndrome
ChiCTR2000030701	10/03/2020	Pending	RCT	Mild and Moderate COVID-19 pneumonia (n=60)	Enoxaparin Sodium + Standard of care	Standard of care	Time to Virus Eradication
ChiCTR2000030700	09/03/2020	Pending	RCT	Mild and Moderate COVID-19 pneumonia (n=60)	Enoxaparin Sodium + Standard of care	Standard of care	Time to Virus Eradication
ChiCTR2000030328	02/03/2020	Pending	Non-RCT	COVID-19 pneumonia (n=60)	Nebulized Heparin-N-acetylcysteine	Placebo	Chest CT; Days of hospitalization; Rate of nucleic acid negativity
ChiCTR2000030089	28/02/2020	Pending	RCT	Several and critical COVID-19 pneumonia (n=60)	Adalimumab + Standard of care	Standard of care	Time to clinical improvement
ChiCTR2000030580	01/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=60)	Adalimumab + Tocilizumab + Standard of care	Standard of care	Chest CT; Time to nucleic acid negativity Immunosuppressive biomarkers test
ChiCTR2000030028	24/02/2020	Pending	RCT	Several and critical COVID-19 pneumonia (n=40)	Anti-programmed cell death-1 monoclonal antibody + Standard of care	Standard of care	Immunosuppressive biomarkers
ChiCTR2000029776	11/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=40)	Polyinosinic-Polycytidylic Acid Injection + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000029974	09/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=300)	Probiotics + Standard of care	Standard of care	Time to clinical recovery

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Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000030007	03/02/2020	Pending	RCT	Mild, moderate, and severe COVID-19 pneumonia (n=200)	Recombinant human granulocyte colony-stimulating factor (5μg/kg) + Standard of care	Standard of care	Clinical symptoms; Blood routine test; Viral load; Immunosuppressive biomarkers test; Chest CT
ChiCTR2000030480	03/03/2020	Recruiting	RCT	COVID-19 pneumonia (n=328)	Interferon α1β (10UG bid for 10 days) + Standard of care	Standard of care	Rate of composite adverse outcomes
ChiCTR2000029989	20/02/2020	Pending	RCT	COVID-19 pneumonia (n=300)	Interferon α1β Eye Drops	Placebo drop	Time to Clinical recovery
ChiCTR2000030167	02/03/2020	Pending	RCT	Mild and Moderate COVID-19 pneumonia (n=80)	Recombinant Human Interleukin-2 (1 million IU per time, qod for 2 weeks) + Standard of care	Standard of care	Immunosuppressive biomarkers test; Mortality; Time to clinical recovery
ChiCTR2000029636	09/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=40)	Recombinant viral macrophage inflammatory protein + Standard of care	NA	Time to nucleic acid negativity
ChiCTR2000029849	01/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=60)	Regulating intestinal flora + Standard of care	Standard of care	Days of hospitalization; Mortality
ChiCTR2000029806	12/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=120)	Group 1: Thymosin (1.6 mg sc qd for 5 days) + Standard of care Group 2: Camrelizumab (200 mg single dose) + Standard of care	Standard of care	Proportion of patients with a lung injury score reduction of 1-point or more 7 days after randomization
ChiCTR2000030779	16/03/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=100)	Ulinastatin + Standard of care	Standard of care	Blood gas; Sequential organ failure assessment
ChiCTR2000030016	04/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=30)	Mycobacterium vaccae injection + Standard of care	Placebo + Standard of care	Time to nucleic acid negativity Mortality; Adverse events; Time to clinical improvement
ChiCTR2000029638	03/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=100)	Nebulization of recombinant super-compound interferon	Nebulization of interferon αIb	Clinical symptoms; Immunosuppressive biomarkers test; Chest CT

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The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; qd: Once a day; bid: twice daily; tid: three times a day; qod: every other day; sc: subcutaneous; CT: computed tomography

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Table 4 Clinical trials of antiparasitic agents for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000029992	17/02/2020	Pending	RCT	COVID-19 pneumonia (n=100)	Group 1: Chloroquine phosphate (1.0g for 2 days; then 0.5g for 12 days); Group 2: Hydroxychloroquine sulfate (0.2g bid for 14 days)	Standard of care	Time to clinical recovery; Viral load
ChiCTR2000030054	22/02/2020	Pending	RCT	Mild and Moderate COVID-19 pneumonia (n=100)	Group 1: Hydroxychloroquine sulfate (0.2g bid for 14 days) Group 2: Chloroquine phosphate (1g for 2 days+ 0.5g for 12 days)	Standard of care	Time to clinical recovery
ChiCTR2000029988	13/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=80)	Chloroquine Phosphate	NA	Time to clinical recovery
ChiCTR2000029975	24/02/2020	Pending	Non-RCT	COVID-19 pneumonia (n=10)	Chloroquine phosphate	NA	Time to nucleic acid negativity; Mortality; Time to clinical improvement
ChiCTR2000029939	10/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=100)	Chloroquine Phosphate + Standard of care	Standard of care	Days of hospitalization
ChiCTR2000029935	06/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=100)	Chloroquine Phosphate+ Standard of care	NA	Days of hospitalization
ChiCTR2000029741	12/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=112)	Chloroquine phosphate	Lopinavir-ritonavir	Mortality; Inflammatory cytokines; Time to nucleic acid negativity
ChiCTR2000029609	10/02/2020	Pending	Non-RCT	COVID-19 pneumonia (n=146)	Mild-moderate patients: Group 1: Chloroquine phosphate Group 2: Lopinavir-ritonavir Group 3: Chloroquine phosphate + Lopinavir-ritonavir Severe patients: Group 1: Chloroquine phosphate Group 2: Lopinavir-ritonavir	NA	Time to nucleic acid negativity
ChiCTR2000029542	03/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=20)	Chloroquine Phosphate	Standard of care	Time to nucleic acid negativity; Mortality
ChiCTR2000030718	12/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=80)	Chloroquine phosphate	Placebo	Time to clinical recovery
ChiCTR2000029559	31/01/2020	Recruiting	RCT	COVID-19 pneumonia (n=300)	Group 1: Hydroxychloroquine (0.1g, bid) Group 2: Hydroxychloroquine (0.2g, bid)	Placebo	Time to nucleic acid negativity
ChiCTR2000029740	11/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=78)	Hydroxychloroquine (0.2g bid)	Standard of care	Time to nucleic acid negativity
ChiCTR2000029868	10/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=200)	Hydroxychloroquine sulfate	Standard of care	Time to nucleic acid negativity
ChiCTR2000029899	17/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=100)	Hydroxychloroquine sulfate (Day1: first dose: 600 mg, second dose: 600mg after 6h; Day2~5: 200mg, bid)	Chloroquine Phosphate (Day1-3: 500mg, bid; Day4-5: 250mg, bid)	Time to clinical recovery

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Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000029898	17/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=100)	Hydroxychloroquine sulfate (Day1: first dose: 600 mg, second dose: 600mg after 6h; Day2-5: 200mg, bid)	Chloroquine Phosphate (Day1-3: 500mg, bid; Day4-5: 250mg, bid)	Time to clinical improvement
ChiCTR2000030029	20/02/2020	Pending	Non-RCT	COVID-19 pneumonia with poorly response (n=20)	Suramin sodium	NA	Clinical cure rate; Mortality

The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; bid: twice daily

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Table 5 Clinical trials of cell-based therapy for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000030835	14/02/2020	Recruiting	Non-RCT	Severe COVID-19 pneumonia (n=20)	Group 1: Mesenchymal stem cells (2 x10^6/kg/ time) + Standard of care Group 2: Low dose: Mesenchymal stem cells (1 x10^6 /kg /time) + Standard of care	NA	NA
ChiCTR2000030138	24/02/2020	Pending	RCT	Severe COVID-19 pneumonia (n=60)	Mesenchymal stem cells	Standard of care	Clinical symptoms
ChiCTR2000030116	01/02/2020	Recruiting	Non-RCT	Acute respiratory distress syndrome of Severe COVID-19 pneumonia (n=16)	Mesenchymal stem cells	NA	Time to leave ventilator
ChiCTR2000030261	01/03/2020	Pending	RCT	COVID-19 pneumonia (n=26)	Mesenchymal stem cells exosomes atomization	Placebo	Chest CT
ChiCTR2000030020	06/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=20)	Mesenchymal stem cells	NA	Rate of nucleic acid negativity; Clinical symptoms; Chest CT
ChiCTR2000029569	05/02/2020	Pending	RCT	Severe COVID-19 pneumonia (n=30)	Mesenchymal stem cells + Standard of care	Standard of care	Pneumonia severity index score; Chest CT
ChiCTR2000030300	20/02/2020	Recruiting	Non-RCT	Critical COVID-19 pneumonia (n=9)	Mesenchymal stem cells	NA	Time to clinical recovery
ChiCTR2000030173	17/02/2020	Pending	RCT	COVID-19 pneumonia (n=60)	Mesenchymal stem cells	Standard of care	Pulmonary function; Rate of nucleic acid negativity
ChiCTR2000030088	01/03/2020	Pending	RCT	Severe COVID-19 pneumonia (n=40)	Mesenchymal stem cells Wharton's Jelly mesenchymal stem cells (1×10^6/kg)	Placebo	Time to nucleic acid negativity; Chest CT
ChiCTR2000029606	25/01/2020	Recruiting	RCT	COVID-19 pneumonia (n=63)	Human Menstrual Blood-derived Stem Cells preparations+ Standard of care	Standard of care	Mortality
ChiCTR2000030944	01/09/2020	Pending	RCT	Severe COVID-19 pneumonia (n=20)	Human natural killer cells-mesenchymal stem cells + Standard of care	Standard of care	Rate of composite adverse outcomes

The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; CT: computed tomography

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Table 6 Clinical trials of plasma therapy for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000030039	31/05/2020	Recruiting	Non-RCT	Moderate, severe and critical COVID-19 pneumonia (n=90)	Convalescent plasma (200-500ml, two infusions) + Standard of care	Standard of care	SARS-CoV-2 DNA; SARS-CoV-2 antibody levels
ChiCTR2000030702	15/02/2020	Recruiting	RCT	Moderate COVID-19 pneumonia (n=50)	Convalescent plasma + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000030627	01/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=30)	Convalescent plasma + Standard of care	Standard of care	Temperature; Virus nucleic acid detection
ChiCTR2000030179	24/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=100)	Convalescent plasma therapy + Standard of care	Standard of care	Clinical cure rate; Mortality
ChiCTR2000029757	14/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=200)	Convalescent plasma + Standard of care	Standard of care	Time to clinical improvement
ChiCTR2000029850	15/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=20)	Convalescent plasma + Standard of care	Standard of care	Mortality
ChiCTR2000030046	07/02/2020	Recruiting	Non-RCT	Moderate and severe COVID-19 pneumonia (n=10)	Anti-2019-nCoV virus inactivated plasma	NA	Clinical symptoms
ChiCTR2000030929	17/03/2020	Pending	RCT	Severe COVID-19 pneumonia (n=60)	Anti-SARS-CoV-2 virus inactivated plasma	Ordinary plasma	Clinical symptoms
ChiCTR2000030010	19/02/2020	Pending	RCT	Severe COVID-19 pneumonia (n=100)	Anti-SARS-CoV-2 virus inactivated plasma	Ordinary plasma	Clinical symptoms
ChiCTR2000030841	17/02/2020	Recruiting	Non-RCT	Severe COVID-19 pneumonia (n=10)	Immunoglobulin of cured patients	Gama-Globulin	Time to clinical improvement
ChiCTR2000029572	05/02/2020	Recruiting	RCT	Severe and critical COVID-19 pneumonia (n=30)	Umbilical plasma + Standard of care	Standard of care	Pneumonia severity index score

The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; SARS-CoV: Severe acute respiratory syndrome-related coronavirus

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Table 7 Clinical trials of anti-inflammatory agents for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrolment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000029656	14/02/2020	Pending	RCT	COVID-19 pneumonia (n=100)	Methylprednisolone injection+ Standard of care	Standard of care	Electrocardiogram; Chest CT
ChiCTR2000029386	29/01/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=48)	Methylprednisolone injection (1-2mg/kg for 3 days)	Standard of care	Sequential organ failure assessment score
ChiCTR2000030481	01/03/2020	Recruiting	RCT	COVID-19 pneumonia (n=200)	Group 1: Early corticosteroid use Group 2: Middle-late corticosteroid use (after 5 days of fever)	Placebo	Time to nucleic acid negativity
ChiCTR2000030170	15/02/2020	Recruiting	Non-RCT	Several and acute exacerbation COVID-19 pneumonia (n=16)	Severe group : Jakotinib hydrochloride (the first 3 subjects were given a dose of 50mg Bid for 7 consecutive days; If no grade ≥3 drug-related adverse effects within 8 days happened, subsequent subjects were given 100 mg bid for 7 day)+Standard therapy Acute exacerbation group: Jakotinib hydrochloride (the first 3 subjects were given a dose of 50mg Bid for 7 consecutive days; If no grade ≥3 drug-related adverse effects within 8 days happened, subsequent subjects were given 100 mg bid for 7 day)+ Standard of care	NA	Severe group: Time to clinical improvement; Acute exacerbation group: Time to clinical recovery
ChiCTR2000030058	10/03/2020	Pending	RCT	COVID-19 pneumonia with poorly responsive Lopinavir-ritonavir (n=200)	Leflunomide	Placebo	Time to nucleic acid negativity
ChiCTR2000030002	15/02/2020	Recruiting	RCT	Moderate, severe and critical COVID-19 pneumonia (n=60)	Tranilast + Standard of care	Standard of care	Clinical cure rate

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Table 8 Clinical trials of additional WMs for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000030892	06/03/2020	Recruiting	RCT	Severe COVID-19 (n=40)	Pirfenidone	Placebo	Pulmonary fibrosis score
ChiCTR2000030333	04/03/2020	Recruiting	RCT	Several and critical COVID-19 pneumonia (n=292)	Pirfenidone (400mg, tid) + Standard of care	Standard of care	Chest CT
ChiCTR2000030539	06/03/2020	Pending	Non-RCT	COVID-19 pneumonia (n=40)	3% hydrogen peroxide gargle	Placebo	Rate of nucleic acid negativity
ChiCTR2000030471	02/03/2020	Recruiting	RCT	Moderate COVID-19 pneumonia (n=394)	Lipoic acid injection + Standard of care	Standard of care	Rate of progression
ChiCTR2000030398	27/02/2020	Pending	RCT	COVID-19 pneumonia (n=340)	Bismuth potassium citrate (2 capsules, bid)	Placebo	Rate of nucleic acid negativity
ChiCTR2000029867	15/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=520)	Carrimycin	Lopinavir-ritonavir	Rate of nucleic acid negativity

The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
WMs : Western medicines; RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; bid: twice daily; tid: three times a day; CT: computed tomography

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Table 9 Clinical trials of WM combination therapy for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control (dosing, if available)	Primary outcome
ChiCTR2000030535	20/02/2020	Recruiting	RCT	Moderate and severe COVID-19 pneumonia (n=100)	Ebastine (10mg bid) + Nterferon-alpha aerosol inhalation (5million U bid) + Lopinavir (200 mg, bid)	Nterferon-alpha aerosol inhalation (5million U bid) + Lopinavir (200 mg, bid)	Clinical cure rate; Chest CT
ChiCTR2000030894	01/03/2020	Recruiting	RCT	Moderate and severe COVID-19 pneumonia (n=150)	Favipiravir +Tocilizumab	Group 1: Favipiravir Group 2: Tocilizumab	Clinical cure rate
ChiCTR2000030987	05/03/2020	Recruiting	RCT	COVID-19 pneumonia (n=150)	Group 1: Favipiravir + Chloroquine phosphatetablets; Group 2: Favipiravir	Placebo	Time to clinical recovery
ChiCTR2000030922	26/02/2020	Recruiting	RCT	Mild and Moderate COVID-19 pneumonia (n=30)	Long-acting interferon alpha-2a (135μg) + ribavirin	Umifenovir + ribavirin	Rate of nucleic acid negativity; Mortality
ChiCTR2000029759	15/02/2020	Temporary halt	RCT	COVID-19 pneumonia (n=60)	Lopinavir-ritonavir+ interferon	Umifenovir +interferon	Time to clinical recovery
ChiCTR2000029387	25/01/2020	Recruiting	RCT	Mild and moderate COVID-19 pneumonia (n=108)	Ribavirin+ Interferon alpha-1b	Lopinavir-ritonavir + Interferon alpha-1b	Time to nucleic acid negativity
ChiCTR2000030262	01/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=30)	Group 1: Anti-viral drugs + Type I interferon + Inflammation inhibitor TFF2 (Once for one day); Group 2: Anti-viral drugs + Type I interferon+ Inflammation inhibitor TFF2 (Once for two days)	NA	Viral load
ChiCTR2000030703	10/03/2020	Recruiting	RCT	Moderate and severe COVID-19 pneumonia (n=40)	Lxekizumab + Antiviral therapy	Antiviral therapy	Chest CT
ChiCTR2000029580	31/01/2020	Recruiting	RCT	Severe and critical COVID-19 pneumonia (n=70)	Mesenchymal stem cells + Ruxolitinib	Standard of care	Safety
ChiCTR2000029600	30/01/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=90)	Group 1: Alpha-interferon atomization Group 2: Lopinavir-ritonavir + Alpha-interferon Group 3: Favipiravir + alpha-interferon atomization	NA	Time to and rate of nucleic acid negativity; Chest CT
ChiCTR2000029431	29/01/2020	Recruiting	RCT	COVID-19 pneumonia (n=45)	Group 1: Ankylosaurus + Standard of care Group 2: Ankylosaurus + Type I macrophages therapy + Standard of care	Standard of care	Chest CT

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The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
WM: Western medicine; RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; bid: twice daily; CT: computed tomography

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Table 10 Clinical trials of TCMs for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Planned date of enrollment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control	Primary outcome
ChiCTR2000029381	24/01/2020	Pending	Non-RCT	Severe COVID-19 pneumonia (n=400)	Xue-Bi-Jing injection	Standard of care	Pneumonia severity index score
ChiCTR2000029432	01/02/2020	Pending	Non-RCT	COVID-19 pneumonia (n=72)	Tan-Re-Qing injection (40ml, qd)	NA	Clinical symptoms (temperature)
ChiCTR2000029756	15/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=238)	Xi-Yan-Ping injection	Alpha-interferon	Clinical symptoms
ChiCTR2000029822	07/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=110)	Honeysuckle decoction	Placebo	Clinical cure rate
ChiCTR2000029855	15/02/2020	Recruiting	RCT	Moderate COVID-19 pneumonia (n=180)	Group 1: Qing-Fei prescription Group 2: Qing-Fei prescription + Compound houttuynia mixture	Standard of care	TCM symptom score; The time and rate of nucleic acid negativity
ChiCTR2000030003	19/02/2020	Pending	RCT	COVID-19 pneumonia (n=480)	Group 1: TCM prescription No. 1 and 2 Group 2: Gan-Ke-Shuang-Qing capsule Group 3: Shuang-Huang-Lian liquid	NA	Days of hospitalization; Clinical symptoms
ChiCTR2000030751	25/01/2020	Pending	Non-RCT	COVID-19 pneumonia (n=60)	Traditional Mongolian Medicine	NA	Chest CT; Time to and rate of nucleic acid negativity
ChiCTR2000030804	01/02/2020	Recruiting	RCT	Moderate COVID-19 pneumonia (n=128)	Exocarpium citri grandis phlegm cough solution	Placebo	
ChiCTR2000030988	23/03/2020	Pending	RCT	Mild and moderate COVID-19 pneumonia (n=204)	Hua-Shi Bai-Du granules	Standard of care	Days of hospitalization

The standard of care followed the guidance of the "Diagnosis and Treatment Protocol for COVID-19 Pneumonia" published by the Chinese National Health Commission [39].
Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
TCM: Traditional Chinses medicines; RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; qd: Once a day; CT: computed tomography

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Table 11 Clinical trials of combination therapy of TCMs and WMs for the treatment of COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Date of enrolment	Recruitment status	Study design	Population (number of patients)	Intervention (dosing, if available)	Control	Primary outcome
ChiCTR2000029434	01/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=240)	Lian-Hua-Qing-Wen Capsules (4 capsules, tid) + Standard of care	Standard of care	Clinical symptoms
ChiCTR2000029589	06/02/2020	Recruiting	Non-RCT	Moderate COVID-19 pneumonia (n=60)	Re-Du-Ning injection + Standard of care	Standard of care	Clinical symptoms(temperature)
ChiCTR2000029605	06/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=400)	Lower dose group: Shuang-Huang-Lian (2 bottles, tid) + Standard of care Lower dose group: Shuang-Huang-Lian (4 bottles, tid) + Standard of care; Lower dose group: Shuang-Huang-Lian (6 bottles, tid) + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000029742	10/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=90)	Moderate patients: Group 1: Sodium Aescinate Injection + Standard of care Severe patients: Group 1: Sodium Aescinate injection + Standard of care	Moderate patients: Group 1: Standard of care Severe patients: Group 1: Standard of care Group 2: Hormonotherapy + Standard of care	Chest CT
ChiCTR2000029768	12/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=60)	Diammonium Glycyrrhizinate Enteric-coated Capsules (150mg, tid) +Vitamin C tablets + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000029769	15/02/2020	Pending	RCT	Severe COVID-19 pneumonia (n=40)	Ba-Bao-Dan (6 capsules, bid) + Standard of care	Standard of care	28-day survival
ChiCTR2000029780	14/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=160)	Shen-Qi-Fu-Zheng injection + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000029781	14/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=160)	Kang-Bing-Du granules + Standard of care	Standard of care	Clinical symptoms(temperature)
ChiCTR2000029813	14/02/2020	Recruiting	RCT	Mild and moderate COVID-19 pneumonia (n=72)	Tan-Re-Qing Capsules (3 capsules, tid) + Standard of care	Standard of care	Time to and rate of nucleic acid negativity Clinical symptoms(temperature)
ChiCTR2000029819	11/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=80)	Ba-Bao-Dan + Standard of care	Standard of care	Viral load; Chest CT; Clinical symptoms
ChiCTR2000029869	10/02/2020	Pending	RCT	COVID-19 pneumonia (n=300)	Truncated Torsion Formula + Standard of care	Standard of care	Chest CT
ChiCTR2000029991	18/02/2020	Recruiting	RCT	Mild and moderate COVID-19 pneumonia (n=72)	Group 1: Ke-Su-Ting syrup (20ml, tid) + Standard of care Group 2: Ke-Qing capsule (3 pills, tid) + Standard of care	Standard of care	Clinical symptoms (cough)
ChiCTR2000029947	01/03/2020	Pending	RCT	COVID-19 pneumonia (n=200)	Qing-Yi No.4 compound + Standard of care	Standard of care	Lung function

ChiCTR2000029954	30/04/2020	Recruiting	RCT	COVID-19 pneumonia (n=300)	Group 1: Honeysuckle oral liquid (60ml each time, tid) + Standard of care Group 2: Honeysuckle oral liquid (180ml each time, tid) + Standard of care	Standard of care	Time to clinical recovery; Pneumonia severity index score
ChiCTR2000029993	20/02/2020	Recruiting	RCT	Mild, moderate and severe COVID-19 pneumonia (n=40)	Liu-Shen Capsule + Arbidol Hydrochloride Tablets+ Standard of care	Standard of care	Clinical symptoms
ChiCTR2000030022	22/02/2020	Pending	RCT	Mild and common COVID-19 pneumonia (n=100)	Pediatric Hua-Tan-Zhi-Ke granules + Standard of care	Standard of care	Time to nucleic acid negativity; Chest CT Rate of progression
ChiCTR2000030043	21/02/2020	Pending	RCT	COVID-19 pneumonia (n=300)	Shen-Fu injection + Standard of care	Standard of care	Pneumonia severity index score; Incidence of new organ dysfunction
ChiCTR2000030117	15/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=348)	Xi-Yan-Ping injection + Standard of care	Lopinavir-ritonavir + Alpha-interferon	Time to clinical recovery
ChiCTR2000030166	25/02/2020	Pending	RCT	COVID-19 pneumonia (n=20)	Qing-Wen-Bai-Du-Yin formula granules + Lopinavir-ritonavir + Interferon α2b injection	Lopinavir-ritonavir + Recombinant human interferon alpha 2b injection	Chest CT
ChiCTR2000030215	26/02/2020	Pending	RCT	COVID-19 pneumonia (n=120)	Group 1: Kang-Guan No. 1 + Standard of care (Mild COVID-19 pneumonia); Group 2: Kang-Guan No. 2 + Standard of care (Moderate COVID-19 pneumonia); Group 2: Kang-Guan No. 3 + Standard of care (Severe COVID-19 pneumonia)	Standard of care	Chest CT
ChiCTR2000030218	22/01/2020	Recruiting	RCT	COVID-19 pneumonia (n=80)	Moderate patients Group 1: Xi-Yan-Ping injection+ lopinavir-ritonavir Severe patients Group 2: Xi-Yan-Ping injection+ lopinavir-ritonavir	Moderate patients Group 1: lopinavir-ritonavir	Time to clinical recovery; Pneumonia Severity Index score
ChiCTR2000030255	01/03/2020	Pending	RCT	Moderate and severe COVID-19 pneumonia (n=300)	Jing-Yin Granule (2 packs, tid) + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000030388	18/02/2020	Recruiting	RCT	Severe COVID-19 pneumonia (n=60)	Xue-Bi-Jing injection (50ml, bid) + Standard of care	Standard of care	Time spent on the ventilator; Mortality; Time to nucleic acid negativity
ChiCTR2000030469	27/02/2020	Recruiting	RCT	Moderate and severe COVID-19 pneumonia (n=96)	Liu-Shen-Wan + Standard of care	Standard of care	Clinical symptoms (temperature)
ChiCTR2000030479	26/02/2020	Pending	RCT	Common COVID-19 pneumonia (n=100)	Yi-Qi-Hua-Shi-Jie-Du-Fang (150mL, bid) + Standard of care	Standard of care	Time to and rate of nucleic acid negativity
ChiCTR2000030490	01/02/2020	Recruiting	Non-RCT	Moderate COVID-19 pneumonia (n=100)	Diammonium glycyrrhizinate enteric-coated capsule + Hydrogen-rich water	NA	Clinical cure rate
ChiCTR2000030518	29/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=60)	Zedoary Turmeric Oil (0.2g, qd) + Standard of care	Standard of care	Time to and rate of nucleic acid negativity; Time to clinical improvement; Chest CT

ChiCTR2000030522	09/03/2020	Recruiting	RCT	COVID-19 pneumonia (n=100)	Ma-Xing-Gan-Shi decoction + Standard of care	Standard of care	Time to clinical recovery
ChiCTR2000030836	01/02/2020	Pending	Non-RCT	Common COVID-19 pneumonia (n=300)	Truncated Torsion Formula + Standard of care	Standard of care	14 days outcome of the subjects; Chest CT
ChiCTR2000030864	01/02/2020	Recruiting	Non-RCT	COVID-19 pneumonia (n=50)	Qing-Fei-Pai-Du decoction + Standard of care	NA	Viral load; Chest CT; Routine TCM symptom score
ChiCTR2000030923	15/02/2020	Recruiting	RCT	COVID-19 pneumonia (n=400)	Group 1: TCM formula 1 or TCM formula 2 (Suspected case); Group 2: TCM formula 3 or TCM formula 4 or TCM formula 5 or TCM formula 6+ Standard of care (confirmed cases);	Group 1: None; Group 2: Standard of care	Clinical symptoms

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Nucleic acid negativity is defined by reverse transcription polymerase chain reaction (RT-PCR)
Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
TCM: Traditional Chinses medicines; RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; qd: Once a day; bid: twice daily; tid: three times a day; CT: computed tomography

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Table 12 Observational studies of pharmacological treatments for COVID-19 in China from the Chinese Clinical Trial Registry

Trial ID	Date of enrollment	Recruitment status	Study design	Population (number of patients)	Exposure (dosing, if available)	Reference (dosing, if available)	Primary outcome
ChiCTR2000030883	18/02/2020	Recruiting	Case series	COVID-19 pneumonia (n=100)	Qing-Fei detoxification decoction (mixture)	NA	Clinical symptom (temprature and respiration); Chest CT; Time to nucleic acid negativity
ChiCTR2000030866	01/02/2020	Recruiting	Case series	Severe and critical COVID-19 pneumonia (n=30)	human umbilical cord derived mesenchymal stem cells ($1\times10^{\wedge}6$ UCMSCs/kg/time on day 0, 3, 6) + Standard of care	NA	Rate of disesae progression; Mortality
ChiCTR2000030854	22/01/2020	Completed	Cohort study	COVID-19 pneumonia (n=237)	GroAbidor + Lopinavir-ritonavir + Recombinant interferon alpha-2b	Lopinavir-ritonavir + Recombinant interferon alpha-2b	Blood routine test
ChiCTR2000030806	01/02/2020	Recruiting	Case series	COVID-19 pneumonia (n=20)	Qing-Fei detoxification soup + ulinastatin (200000 U Bid)	NA	Blood routine test
ChiCTR2000030389	29/02/2020	Recruiting	Cohort study	COVID-19 pneumonia (n=120)	Triple energizer treatment + Standard of care	Standard of care	Chest CT; TCM symptoms
ChiCTR2000029637	07/02/2020	Pending	Cohort study	COVID-19 pneumonia (n=100)	Xin-Guan-1 formula + Standard of care	Standard of care	Time to remission and disappearance of primary symptoms

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Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
TCM: Traditional Chinses medicines; WM: Western medicines; RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; CT: computed tomography

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Table 13 Published results of clinical trials conducted in China

Author year	Population (number of patients)	Study design	Intervention/Exposure (dosing, if available)	Comparator/Reference (dosing, if available)	Primary outcomes
CNKI					
Fu 2020 [12]	COVID-19 pneumonia (n=37)	RCT	Tou-Jie-Qu-Wen granules (bid, 15 days) + Umifenovir (200 mg, tid, 10 days)	Umifenovir (200 mg, tid, 10 days)	Significant improvement in TCM syndrome score, the absolute value of lymphocyte, C reactive protein value (P<0.05)
Wang 2020 [13]	Moderate COVID-19 pneumonia (n=60)	RCT	Lopinavir-ritonavir (400 mg/100 mg, bid, 7-10 days) + Lian-Hua-Qing-Wen capsule (4 tablets, tid) + Interferon-α (500 million units, bid)	Lian-Hua-Qing-Wen capsule (4 tablets, tid) + interferon-α (500 million units, bid)	Effective rate of treatment: 76.67% vs 46. 67%, P<0.01
Chen 2020 [14]	Moderate COVID-19 pneumonia (n=30)	RCT	Hydroxychloroquine (400, qd for 5 days) +Standard treatment	Standard of care	Rate of RP-PCR negative: 86.7% vs 93.3%, P>0.05
MEDLINE					
Cao 2020 [15]	COVID-19 pneumonia (n=199)	RCT	Lopinavir–ritonavir (400 mg/100 mg, bid for 14 days) + Standard of care	Standard of care	Hazard ratio for clinical improvement: 1.24; Difference of mortality at 28 days: 19.2% vs. 25.0%, P>0.05
WHO database					
Yuan 2020 [16]	COVID-19 pneumonia (n=67)	RCT	Lopinavir-ritonavir combined + IFN-α + Ribavirin	Lopinavir-ritonavir + IFN-α	Time to RP-PCR negative and days of hospitalization: no significant difference, p>0.05
MedRxiv and BioRxiv					
Chen 2020 [17]	COVID-19 pneumonia (n=62)	RCT	Hydroxychloroquine (400 mg/d) + Standard of care	Standard of care	Significant improvement in time to clinical recovery (temperature recovery time and the cough remission time); larger proportion of patients with improved pneumonia (80.6% vs 54.8%)
Li 2020 [18]	Mild or moderate COVID-19 pneumonia (n=44)	RCT	Group 1: Lopinavir-ritonavir (400 mg/100 mg, bid for 7-14 days) Group 2: Umifenovir (200mg, tid for 7-14 days)	Standard of care with no antiviral medicine	No significant difference in median time of positive-to-negative conversion of SARS-CoV-2 nucleic acid (8.5 vs 7 vs 4, P=0.751); No statistical differences in the rates of antipyresis, cough alleviation, improvement of chest CT or the deterioration rate of clinical status (all P > 0.05)
Chen 2020 [19]	COVID-19 pneumonia (n=236)	RCT	Favipiravir (Day1: 1600 mg, bid; following days: 600mg, bid) + Standard of care	Umifenovir (200 mg, tid) + Standard of care	Moderate patients: significant improvement in clinical recovery rate of day 7 (71.43% vs 55.86%, P=0.0199); Significant fever reduction and cough relief (P<0.001); More adverse events (13.79% vs 2.50%, P<0.0001)

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Rate of composite adverse outcomes is defined as SpO2<= 93% without oxygen supplementation, or PaO2/FiO2 <= 300mmHg, or respiratory rate (RR) <=30 breaths per minute
Time to clinical recovery is defined as the normal body temperature (underarm temperature <= 36.9 degrees C) and cough relief (evaluated by the cough symptom score scale) in the duration of at least 72 hours from the start of study treatment
RCT: Randomized clinical trial; COVID-19: Coronavirus Disease 2019; NA: Not available; qd: Once a day; bid: twice daily; tid: three times a day; CT: computed tomography; SARS-CoV: Severe acute respiratory syndrome-related coronavirus

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Table 14 Published results of observational studies conducted in China

Author year	Population (number of patients)	Study design	Intervention/Exposure (dosing, if available)	Comparator/Reference (dosing, if available)	Primary outcomes
CNKI					
Shi 2020 [20]	COVID-19 pneumonia (n=49)	Cohort study	TCMs + WMs	WMs	Significant differences in hospitalization days and clinical symptom score (P < 0.05)
Xia 2020 [21]	COVID-19 pneumonia (n=52)	Cohort study	TCMs + WMs	WMs	Significant improvement in clinical syndrome, cure rate, hospitalization time (P<0.05)
Qu 2020 [22]	COVID-19 pneumonia (n=70)	Cohort study	Shu-Feng-Jie-Du Capsule (2.08g, tid,10 days) + Umifenovir (0.2g, tid)	Umifenovir (0.2g, tid)	Significant differences in symptom improvement (P < 0.05); Significant differences in negative conversion time (P < 0.05)
Chen 2020 [23]	COVID-19 pneumonia (n=134)	Cohort study	Group 1: Lopinavir-ritonavir (400 mg/100 mg, bid, 5 days) + interferon-α2b + symtom treatment (n=52) Group 2: Umifenovir (200 mg, tid, 5 days) + interferon-α2b + symtom treatment (n=34)	Interferon-α2b + symptom treatment (n=48)	Rate of RP-PCR negative: 71.8%vs 82.6% vs 77.1%, P= 0.79; Number of patients of CT after 7 days treatment still in progress: 22 vs 13 vs 25, P=0.3
Cheng 2020 [24]	COVID-19 pneumonia (n=54)	Case series	Lian-Hua-Qing-Wen (1 pack, tid) + conventional treatments	NA	The days of symptoms disappearance in fever, weakness, and cough was 3. 6 ± 2. 14 days, 4. 1 ± 2. 58 days, and 5. 3 ± 2. 63 days; The rate of symptoms disappearance in the chest stuffiness, the dyspnea and the moist crackles was 84. 6%, 100% and 89. 5%; The total efficiency was up to 81. 6% without any observed side effects by the seventh day.
Lu 2020 [25]	COVID-19 pneumonia (n=101)	Case series	Lian-Hua-Qing-Wen Granules (6g, tid) + Standard of care	NA	Remission rate of fever: 86.7% vs. 67.6%,P= 0.03; Remission rate of cough: 55.6% vs. 30.6%, P=0.02; Remission rate of fatigue: 82.5% vs. 58.6%, P=0.03, Remission rate of dyspnoea: 68.2% vs. 20%, P=0.002; Duration of fever: 6 days vs. 7 days, P= 0.17
Yao 2020 [26]	COVID-19 pneumonia (n=21)	Case series	Lian-Hua-Qing-Wen Granules + Standard of care	NA	Remission rate of fever 85.: % vs. 57.1%, P =0.04; cough: 46.7% vs. 5.6%, P ¼ 0:01; Remission rate of expectoration: 64.3% vs. 9.1%, P=0.01; Remission rate of shortness of breath: 77.8% vs. 0, P=0:02; Duration of fever: 4.6 ±3.2 vs. 6.1 ±3.1 days, P=0.22
National Administration of Traditional Chinese Medicine, 2020 [27]	COVID-19 pneumonia (n=214)	Case series	Qing-Fei-Pai-Du Decoction + Standard of care	NA	Effective rate: 90%; Improvement in radiology:60%
Guangdong Medical Products Administration, 2020 [28]	COVID-19 pneumonia (n=50)	Case series	Tou-Jie-Qu-Wen Granules + Standard of care	NA	Remission rates of cough: 50%; Remission rates of sore throat: 52.4%; Remission rates of fatigue: 69.6%

Yu 2020 [29]	COVID-19 pneumonia (n=25)	Case series	Lopinavir-ritonavir (400 mg/100 mg, bid) + interferon-α2b (500 million units, bid)	NA	21 patients were improved; 1 patient was cured 2 patients were exacerbated; 1 patient was dead
Xu 2020 [30]	COVID-19 pneumonia (n=49)	Case series	Lopinavir-ritonavir (400 mg/100 mg, bid) + Abidor tablets (200 mg, tid)	NA	First time to nucleic acid negativity: 12 days
Zhu 2020 [31]	COVID-19 pneumonia (n=23)	Case series	Lopinavir-ritonavir + interferon-α + Moxifloxacin + TCM	NA	Time to nucleic acid negativity: 11.6 ± 0.8 days
Gao 2020 [32]	COVID-19 pneumonia (n=40)	Case series	40 patients: Lopinavir-ritonavir (400 mg/100 mg, bid)+ interferon-α2b (500 million units, bid) 11 patients: Umifenovir (0.2 g, tid) 8 patients: Oseltamivir capsules (75 mg, bid); 16 patients: Ribavirin injection (0.5g, qd); 25 patients Antibiotics; 6 patients: methylprednisolone (40~80 mg, bid)	NA	All patients were improved; 14 patients were cured
Wei 2020 [33]	Moderate and severe COVID-19 pneumonia (n=463)	Case series	93 patients: Lopinavir-ritonavir; 220 patients: One or two of 1 or 2 of antiviral therapy (oseltamivir, umifenovir or ribavirin) 42 patients: Alpha-interferon nebulization; 406 patients: Anti-infection drugs; 49 patients: Heparin; 96 patients: glucocorticoids; 63 patients: TCMs	NA	463 patients were cured; days of hospitalization: 12 days, 13 days for severe group, 11 days for moderate group
Li 2020 [34]	Severe COVID-19 pneumonia (n=217)	Case series	125 patients: Lopinavir-ritonavir (400 mg/100 mg, bid) 71 patients: Lopinavir-ritonavir (400 mg/100 mg, bid) + Abidor tablets 22 patients: Lopinavir-ritonavir (400 mg/100 mg, bid) + interferon-α	NA	180 patients were cured and 27 patients were dead.
MEDLINE					
Duan 2020 [35]	Severe COVID-19 pneumonia (n=10)	Case series	Convalescent plasma (200mL) + Antiviral agents	NA	No severe adverse effects; Improvement of clinical symptoms and laboratory parameters within 3 d after convalescent plasma transfusion
WHO database					
Deng 2020 [36]	COVID-19 pneumonia (n=33)	Cohort study	Umifenovir + Lopinavir-ritonavir	Lopinavir-ritonavir	Rate of RP-PCR negative: 75% vs 35%, P<0.05; Improvement in chest CT: 69% vs 29%, P<0.05
MedRxiv					

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Bian 2020 [37]	COVID-19 pneumonia (n=28)	Cohort study	Meplazumab (10mg on day 1, day 2 and day 5) + Standard of care	Standard of care	Significant improvement in the discharged (p=0.006) and case severity (p=0.021) in critical and severe patients; Significant reduce in the time to virus negative (p=0.014); Improvement in the percentages of patients recovered to the normal lymphocyte count and CRP concentration; No adverse events

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