

A survey of 434 clinical trials about coronavirus disease 2019 in China

To the Editor,

As of 15 March 2020, 81 059 cases were diagnosed totally in China, including 10 817 patients receiving treatments and 3226 severe cases. Currently, there are no effective antiviral medications or vaccines available.¹ However, many clinical trials about coronavirus disease 2019 (COVID-19) are undergoing to find effective treatment in China, which has not been reported.

On 15 March 2020, we used “novel coronavirus” or “coronavirus disease 2019” or “COVID-19” in Chinese language to search in the Chinese Clinical Trial Registry database without time limitation (<http://www.chictr.org.cn/index.aspx>). We analyzed these records according to the date, geographical distribution, the objective of study, study type and design, and sample size to reveal the current situation of the clinical trials about COVID-19 in China.

434 registered clinical trials about COVID-19 were enrolled. The first record was from Wuhan Jinyintan Hospital on Jan 23, where has been the core battlefield to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the early stage. It was a randomized, open-label, blank-controlled trial for the efficacy and safety of lopinavir-ritonavir and interferon-alpha 2b in hospitalization patients with COVID-19. Two thirds of the total records occurred from Feb 12 to Mar 3 with a mean speed of (12 ± 4) records per day (Figure 1A). The number of the registered records trended to decrease since 4 March. A total of 130, 49, 37, and 35 records located in Hubei, Guangdong, Shanghai, and Sichuan, respectively, turning to be the top four provinces (Figure 1B). Furthermore, the top five cities belonged to Wuhan, Shanghai, Beijing, Chengdu, and Guangzhou with the records of 117, 37, 32, 31, and 29, respectively.

We unfolded the objectives of trials according to cell therapy (19 records), biological therapy (34 records), western medicine (71 records), Chinese medicine (99 records), and others (211 records). Mesenchymal stem cells (MSCs) were the most popular seed cells with 14 records followed by NK cells and mononuclear cells with 3 and 2 records, respectively. As for the biological therapy, 16 clinical trials focused on anti-cytokine storm occurring in severe patients, like recombinant interferons recommended by the National Health Commission of China, anti-tumor necrosis factor- α , anti-interleukin-6, and anti-GM-CSF. Seven clinical trials were going to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of patients with COVID-19. Of the 71 records related to the western medicine, remdesivir captured the public's attention very much.² The other antiviral medications involved phosphoric chloroquine (23 records) and lopinavir-ritonavir (17 records), which were also clinically used in the treatment now. Many kinds of Chinese traditional

medicine or methods were under evaluation. The others were mainly about mental health of the patients, doctors, nurses, college students, the public, and the other kinds of diagnosis methods, like the lung ultrasound. None of specific vaccines are in the clinical trial stage.

As for the study type, 221 of the 434 records belonged to the interventional research. 121 clinical trials were observational studies. 18 trials aimed to the diagnostic tests. Researchers were exploring several kinds of diagnostic methods including new high-throughout detection of SARS-CoV-2 nucleic acid (4 records), plasma immunoglobulin M/immunoglobulin G detecting (3 records), chest computed tomography imaging (3 records), lung ultrasound (2 records), sputum or throat swab sample collecting (2 records), screening of peripheral blood biomarkers (2 records), screening of microRNAs as early diagnostic markers of COVID-19 viral infection (1 record), and magnetic resonance imaging for myocardial damage diagnosis (1 record). The top four kinds of study design were parallel, sequential design, non-randomized control, and single arm with the number of 168, 110, 31, and 27 records, respectively. The sum of the samples of all clinical trials about COVID-19 was 254,635. However, despite 202,842 objects without COVID-19 themselves, 51 793 patients with COVID-19 will be enrolled into the related 327 clinical trials.

We also used “2019-nCoV” or “SARS-CoV-2” or “novel coronavirus” or “coronavirus disease 2019” or “COVID-19” in English language to search in the clinicalTrials.gov. 94 records were obtained, and most of them are the same as those registered in the Chinese Clinical Trial Registry database. 16 records were from out of China mainland, namely France (5 records), United States (3 records, namely 2 for remdesivir, and 1 for Vaccine-mRNA-1273), South Korea (3 records, namely 2 for remdesivir and 1 for lopinavir/ritonavir), Hong Kong (2 records), Thailand (1 record), and Italy (1 record).

The Chinese doctors and researchers showed great power to respond to an urgent health problem by setting 434 clinical trials in 52 days. However, a strict designed protocol is a guarantee for the believable result, especially for the parallel randomized trials. Of the 221 interventional trials, only 19 trials (8.5%) have a good designed protocol according to the standard protocol items: recommendations for interventional trials.³ Compared with the trials set outside of China mainland, another problem is that 55.1% of the 434 trials did not claim to use the right data management system including a paper case record form and an electronic data capture. Meanwhile, a big concern occurs that is 10 817 patients are receiving treatments in hospital and only few new cases are diagnosed nowadays (Figure 1C), while 51 793 patients with COVID-19 are needed in the trials. Further analysis showed that 209 trials were recruiting, 201 trials were not yet recruiting,

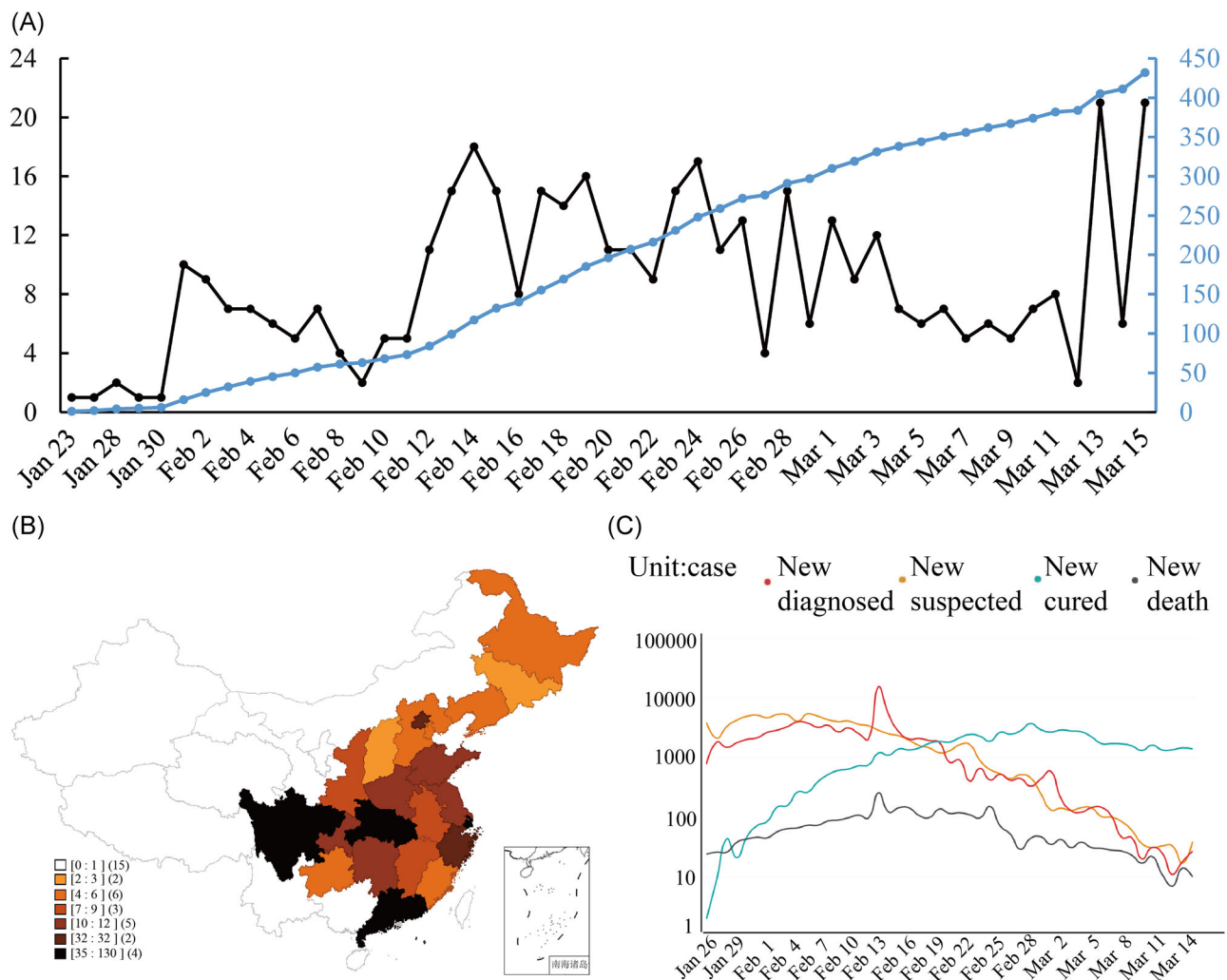


FIGURE 1 A, Distribution of the 434 clinical trials about COVID-19 according to the date and (B) geographical distribution. C, The epidemic trend of COVID-19 in China. COVID-19, coronavirus disease 2019

13 trials were suspended because of lack of patients and only 11 were completed. None of the completed trials belonged to interventional study. The possible solution is to integrate the similar trials and meanwhile, select some trials of top priority. Considering to the pathogenic mechanism of SARS-CoV-2,^{4,5} we deemed carefully that the anti-SARS-CoV-2 inactivated convalescent plasma, MSCs transplantation,⁶ remdesivir, and tocilizumab⁷ are the most four promising alternatives currently in the treatment of the patients with COVID-19, especially for the severe and critically severe types. Furthermore, we have primarily demonstrated that transplantation of ACE2⁺ MSCs improves the outcome of patients with COVID-19 pneumonia by revering the lymphocyte patten and regulate the cytokine storm.⁶

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