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Chinese Guidelines related to Novel Coronavirus Pneumonia

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Abstract

Background and Objective: China has managed to control the coronavirus disease (COVID-19) with confinement measurements and treatment strategies, while other countries are struggling to contain the spread. This study discusses the guidelines related to COVID-19 in China in order to provide important references for other countries in the fight against COVID-19.

Methods: Chinese guidelines relevant to COVID-19 were systematically searched via the China National Knowledge Infrastructure database, YiMaiTong database, and World Health Organization (WHO) COVID-19 database on March 20th, 2020. Guideline information was extracted, including date of publication, source, objectives and the target population. Guidelines specific to the pharmacological treatment of COVID-19 were further investigated to identify the types of antivirus drugs recommended and to report on how treatment recommendations for COVID-19 have evolved overtime.

Results: A total of 114 guidelines were identified, of which 87 were national guidelines and 27 were regional guidelines. The scope of included guidelines consisted of: the diagnosis and treatment of COVID-19, the management of hospital departments and specific diseases during the outbreak of COVID-19. Sixty-four of the included guidelines targeted all COVID-19 patients, while the remaining guidelines concentrated on special patient populations (i.e., geriatric population, pediatric population, and pregnant population) or patients with coexisting diseases. Twenty-three guidelines focused on the pharmacological treatments for all COVID-19 patients. Interferon, Lopinavir/Ritonavir, Ribavirin, Chloroquine, and Umifenovir represented the most recommended antivirus drugs. With the emergence of encouraging results from preclinical and preliminary clinical studies, Chloroquine Phosphate was recommended in the national Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th version) on February 19th, 2020. Thereafter, more detailed guidelines regarding the adjustment of dosage regimens and the monitoring of adverse events of Chloroquine Phosphate were published. To date, 8 Chinese guidelines have recommended Chloroquine Phosphate or Hydroxychloroquine as mainstream antivirus drug for the treatment of COVID-19.

Conclusions: China has generated a plethora of guidelines covering almost all aspects of COVID-19. Chloroquine, as one widely affordable treatment, holds great potential to become the gold standard choice as more clinical evidence is shared by researchers from China as well as other countries.

Keywords: Chinese Guidelines; COVID-19; Pharmaceutical Treatment

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1. Introduction

In late December of 2019, the first pneumonia case with unknown microbial origin was reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named as the 2019 novel coronavirus (2019-nCoV), and finally named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), now commonly referred to as COVID-19 [1]. Although the number of newly infected cases per day appeared to decline within China, including the Hubei province [2], the number of COVID-19 cases outside China increased drastically. Concerned by its alarming levels of global spread and severity, COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020 [3].

COVID-19 initially spread quickly to neighboring Asian countries, with South Korea being the most affected [4]. Following this, a sharp growth in confirmed cases was witnessed in Europe, with many European countries reporting nation-wide community transmission; thus, rendering Europe the most affected world region of the pandemic. However, the United States (US) began to report tens of thousands of new cases beginning on March 24th, 2020, eventually exceeding the 123,776 confirmed cases in China recorded on March 29th, 2020, therefore, rendering the US the new center of the pandemic [5].

As of March 28th, 2020, 82,230 patients have been identified as infected by SARS-COV-2 in China, with a total of 3,301 deaths [2]. Based on the data available, as of the 17th of March 2020, the overall fatality rate was 7.2% for confirmed COVID-19 cases in Italy [6], which was much higher than the observed fatality rate of 2.7% in mainland China[7]. This could be due to factors, such as Italy's high proportion of older patients confirmed with COVID-19 and patients with mild symptoms no longer being tested beginning on the 25th of February 2020 and no longer being accounted for. Although the accurate estimation of mortality rate is unavailable as the denominator is impossible to assess, the absolute number of deaths is relatively high. However, comparisons in mortality rates between countries also depend on how cases are counted, which varies by country.

According to the largest retrospective study consisting of 44, 672 confirmed cases published by the Chinese Center for Disease Control and Prevention, older patients and patients with comorbidities, including cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer, were all associated with an increased risk of death [8]. A high Sequential Organ Failure Assessment (SOFA) score and d-dimer >1μg/mL could be important indicators for poor prognosis at an early stage [9].

The outbreak seems to be under control in China as several provinces have declared no infected cases remain. However, the rapid expansion of COVID-19 is still ongoing in Europe. The number of COVID-19 infections and deaths in Europe has not yet peaked, despite approximately 16,000 deaths already across Italy, Germany, and France as of the 29th of March 2020 [2].

Therefore, it may be insightful to understand the Chinese experience and what guidelines have been established to control the spread of COVID-19. Guidelines related to patient channeling, the organization of the health care system, patient triage, and patient investigations may not be transferable due to inherently different healthcare systems in different countries. The authors have focused on the specific pharmacological guidelines for the treatment of COVID-19. The objective of this manuscript is to identify and describe the pharmaceutical guidelines developed in China and to analyze adjustments in the treatment of COVID-19 over time based on the increasing experience in treating COVID-19 patients.

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2. Method

Database search

The China National Knowledge Infrastructure (CNKI) database was searched on the 20th of March 2020 to identify guidelines relevant to COVID-19. The following keywords were used: Novel Coronavirus Pneumonia, COVID-19, SARS-CoV-2, expert consensus, guideline, guidance, recommendation, advice, standard pathway, and clinical pathway. Additionally, YiMaiTong database, as one of the most prestigious databases for collecting healthcare information in China, was also complementarily searched in order to identify guidelines potentially published in grey literature. The WHO database of publications on COVID-19 was also searched to ensure all important guidelines were identified, collected, and analyzed. For guidelines with updated versions with the generation of new evidence, all guideline versions were included.

Data extraction and guidelines classification

The following characteristics of included guidelines were extracted: 1) date of publication, 2) source of the guidelines, 3) objectives of the guidelines, and 4) target population of the guidelines.

Guidelines were classified according to the objectives of the guidelines, which were the main aspects relating to COVID-19. These included: 1) prevention and control, 2) diagnosis, 3) treatment, 4) prevention and treatment, 5) diagnosis and treatment, 6) Traditional Chinese Medicine (TCM) Physiotherapy (e.g. acupuncture and exercise rehabilitation), 7) pharmacy service, 8) nutrition regime, 9) management of patients with specific diseases (e.g. Parkinson's disease, myocardial infarction, and melanoma etc.) under the outbreak of COVID-19, 10) management of specific hospital departments (e.g. cardiology department and pulmonology department) under the outbreak of COVID-19.

The target populations of the COVID-19 guidelines were further categorized: 1) all patients with COVID-19, 2) patients with a certain degree of severity of COVID-19, including suspected cases and confirmed cases (mild cases, severe cases, and critical cases), 3) special populations, including the geriatric population, pediatric population, and pregnant population, 4) patients with specific diseases, such as oncology and cerebrovascular disease.

Moreover, the treatments of COVID-19 were further classified into: 1) TCM therapies, 2) Western Medicine (WM) ,3) Integrative Chinese Medicine (ICM) therapies, which referred to as the combined treatment of TCM and western medicines, 4) other therapies, such as the convalescent plasma therapy. Considering the diversity in the names of TCMs, only the TCMs with brand names were investigated in this study. TCM, WM, and ICM were regarded as pharmacological treatments and were extracted to investigate what medicines were most recommended in the treatment of COVID-19 patients.

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3. Result

Overview of included guidelines

Among the total of 114 published guidelines identified, 22 of them were published in January of 2020, 64 of them were published in February of 2020, and 28 of them were published in March of 2020 (Figure 1). Considering the national and regional source of the included guidelines, 88 of them were national guidelines, which were mainly published by the National Medical Association of China (Figure 2), including the National Health Commission and national associations for varying medical subjects, such as the Respiratory Branch of Chinese Medical Association. Twenty-seven of the included guidelines were regional guidelines. The principle of developing regional guidelines was generally consistent with the national guidelines, with reasonable adjustments included by considering local social circumstances, disease epidemiology, and treatment experience. Regional guidelines (N=27) were released by 8 provinces and 2 municipalities released. All of these provinces, except for Shanxi province and Liaoning province, were severely afflicted areas and were among the top 15 regions with the largest number of infected cases in China. The provinces of Hubei and Guangdong were the regions reporting the largest and second-largest number of confirmed cases and published the greatest number of regional guidelines. Beijing and Shanghai both released their clinical pathways for the diagnosis and treatment of COVID-19 due to their powerful roles in research and academia in China.

Scope of included guidelines

The diagnosis and treatment of COVID-19 was the most-discussed subject in all of the published guidelines (Figure 3). Management of special hospital departments during hospital outbreaks was paramount to ensure the routine practice in these special departments was not disrupted. Management of the emergency department, surgery department (e.g, cerebrovascular surgery, colorectal surgery, and articulation surgery), and intensive care units were most targeted. Management of patients with specific diseases was also covered extensively. For example, patients with acute myocardial infarction (AMI) were transported to designated hospitals to ensure timely thrombolysis therapy, therefore, following slightly different, yet maintained clinical pathways. Expert consensus for COVID-19 patients also diagnosed with Parkinson's disease was available to provide recommendations on the dosage adjustment for anti-Parkinson's medicines as well as on the strategies to prevent secondary bacterial infection among severe or critical patients. Guidelines on providing recommendations for key pharmacy service, such as handling the abundant supply of COVID-19 medicine, the control of donated medicine, the report of adverse effects, and the process for therapeutic drug monitoring, were also available. Nutrition guidelines, especially for severe and critical cases, provided important instructions related to energy intake, nutrition regimes, and nutrition evaluation in order to prevent the occurrence of malnutrition in COVID-19 patients. Guidelines on rehabilitation with TCM were developed to standardize its appropriate application and to alleviate the patients' symptoms, such as Tai Chi, acupuncture, massage, and cupping therapy. Other guidelines investigated the management of medical protective equipment and retail pharmacy, postponement of immunization, and psychological intervention for public panic.

Included guidelines and target patient populations

More than half of the guidelines applied to all patients affected by COVID-19 (Figure 4), 5 guidelines applied to severe and critical cases, 2 guidelines applied to suspected cases, and 2 guidelines applied to convalescent cases. Seven guidelines discussed the prevention and control of COVID-19 in children, from wearing pediatric medical masks, observations of changes in daily activity, to the education on appropriate use of medicines. Six guidelines concentrated on the management of COVID-19 in pregnant women, including psychological counseling, the selection of drugs with lower pregnancy risks, and the assessment of patients' conditions to terminate the pregnancy. Only one guideline specifically targeted elderly patients, partly because elderly patients were largely covered in the severe and critical COVID-19 cases. Twenty-seven guidelines focused on COVID-19 patients with

coexisting diseases., where patients with cardiovascular diseases and cancer fostered the largest part of discussions.

Pharmacological treatments for COVID-19

A total of 23 guidelines focusing on pharmacological treatments for all COVID-19 cases were further investigated (**Error! Reference source not found.**), including 7 versions [10-15] of the 'Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia' released by the National Health Commission, 5 rapid advice guidelines [16-20] developed by 2 influential hospitals (TongJi hospital and ZhongNan hospital) in Hubei province, 4 regional guidelines [21-24] released in Beijing, Shanghai, Shandong province, and Guangdong province, 5 guidelines [25-29] for the appropriate use of TCM in the treatment of COVID-19, and 3 guidelines [22, 30, 31] specific to the optimal use of Chloroquine Phosphate.

In guidelines discussing treatments for COVID-19 (N=15, excluding guidelines specific for TCM and for Chloroquine Phosphate), antivirus therapies were regarded as the general pharmacological treatment for all COVID-19 patients. However, all 15 guidelines outlined that there were no 'specific antivirus medicines' to eradicate the SARS-CoV-2 infection and to show 100% effectiveness in all patients across different disease stages. Interferon (IFN) was recommended in 14 guidelines, with the exception of one Beijing guideline. IFN-α was the only IFN-type medicine recommended in 13 guidelines, except for the Shanghai guideline, which recommended IFN-k as first choice and IFN-α as second choice. Lopinavir/Ritonavir was recommended in 14 guidelines, with the exception of the Shanghai guideline. Ribavirin was recommended in 7 guidelines published after February 1st of 2020, with the exception of the Shanghai guideline. Chloroquine Phosphate was first recommended in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th version) on the 19th of February 2020, 5 guidelines published afterwards included Chloroquine medicines. The Shanghai guideline recommended both Hydroxychloroquine (first choice) and Chloroquine Phosphate (second choice), the Shandong guideline recommended Hydroxychloroquine only, and 3 guidelines recommended Chloroquine phosphate only. Umifenovir was first recommended in the rapid advice guidelines (1st edition) published by the Tongji hospital on the 22nd of January 2020, but it was not included in the national Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia until the 19th of February 2020. Umifenovir was then recommended in 4 guidelines published after the National Protocol. Other antivirus medicines, Oseltamivir and Remdesivir, were recommended in the rapid advice guidelines published by the TongJi hospital on the 22nd of January 2020 and by the ZhongNan hospital on the 1st of February 2020.

With regards to TCM therapy for COVID-19 treatment, the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (7th version) recommended 5 TCM oral preparations during a medical observation period, 5 TCM injections for severe cases, and 7 TCM injections for critical cases. All other included guidelines specific to TCM treatments added several TCM treatments to those recommended by the national protocol, with the number of additional TCM treatments ranging from 1 (the Shangxi guideline) to 13 (the Beijing guideline). For mild cases, Reyanning injection, Shuanghuanglian oral liquid, and Siji kangbingdu injection were recommended in more than 2 TCM guidelines. For severe cases, Angong niuhuang capsules and Suhexiangwan were recommended in more than 2 TCM guidelines.

Other pharmacological treatments were recommended for use depending on the severity of COVID-19 and other coexisting disorders secondary to COVID-19. These treatments included: 1) short-term corticosteroid therapy recommended for patients who demonstrated progressively deteriorating oxygenation index, rapid imaging progression, and overactive inflammatory responses, 2) antibiotic therapy, with inappropriate use of antibiotic therapy being avoided, and caution taken in combinations with broad-spectrum antibiotics, and 3) Tocilizumab, as an immunosuppressive agent, which was first recommended in the Diagnosis and Treatment Protocol for Novel

Coronavirus Pneumonia (7th version) on the 4th of March 2020, and then included in the Guangdong guideline on the 10th of March 2020.

The Diagnosis and Treatment Protocol for COVID-19

The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (referred to as the Diagnosis and Treatment Protocol) was issued by the National Health Commission of the People's Republic of China. As the most important national guideline in China, it offers comprehensive information related to COVID-19, including the etiology, epidemiology, pathology, clinical characteristic, diagnosis, treatment, criteria for recovery, and monitoring after hospital discharge.

The Diagnosis and Treatment Protocol has been updated as additional research evidence and knowledge on COVID-19 have become available. Since the release of the first version of the protocol on January 15th, 2020, updated versions have been published. Over a 50-day period, from the publication of the first version until the latest version published, 7 versions in total have been produced, with 8 updates – 8 updates are recorded as the fifth version of the protocol underwent 2 updates[12, 13].The rate at which the protocol was updated has been unprecedented with new versions being published within days to 2 weeks from the preceding versions – Table 2 includes the details of publishing dates [10-15]. The first and second versions of the Diagnosis and Treatment Protocol are currently not published on the official website. Therefore, this manuscript focuses on the analysis of the available versions, versions 3~7.

TCM Recommendations for COVID-19

Beginning with version 3 of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia, the inclusion and elaboration on the use of TCMs in the Diagnosis and Treatment Protocol have been gradually improved. The Diagnosis and Treatment Protocol determined that COVID-19 met the definition of plague caused by the epidemic pathogenic factors from the perspective of TCM. It was stressed in the protocol that TCM treatment regimens for COVID-19 should be adjusted according to the varying local climate characteristics, individual state of illness, and physical conditions [10]. The 3rd version of the protocol states that the choice of TCMs should be made based on patient symptoms, such as dampness, heat, poison, and stasis of the lung, yet no recommendations were given on the specific TCMs to be used [10].

The 4th protocol version introduced a selection of recommended TCMs to be used either in a medical observation period where patients were only suspected cases of COVID-19 or in a clinical treatment period where patients were confirmed cases of COVID-19 [11]. Four kinds of TCM oral preparations were recommended in the medical observation period, including Huoxiangzhengqi (pills, liquid, or oral solution), Jinhuaqinggan (granules), Lianhuaqingwen (granules), and Shufengjiedu (granules). For patients in the clinical treatment period the recommendations for use of TCM were further divided based on clinical manifestations during 4 subperiods. These subperiods included the mild subperiod characterized by cold and damp stagnation lung syndrome, the moderate subperiod presenting plague poison and lung-closing syndrome, the severe subperiod identified by syndrome of inner blocking causing collapse, and the convalescent subperiod showing lung and spleen qi deficiency syndrome. No TCM injection was recommended for the mild subperiod. Two kinds of TCM injections, Xiyanping injection and Xuebijing injection, were recommended for treatment during the moderate subperiod, and three kinds of TCM injections, Xuebijing injection, Shenfu injection, and Shengmai injection, were recommended for treatment during the severe subperiod.

No changes in the recommendations of use and types of TCMs for the treatment of COVID-19 were made in either of the 2 updates of the 5th version of the protocol.

The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia's 6th protocol version added lung cleansing and detoxifying decoction as a general prescription for the clinical treatment period. The 6th protocol version redefined the subperiods characterizing the clinical treatment period and further divided it into 5

subperiods. The five subperiods of the clinical treatment period were based on disease severity and included mild subperiod (cold dampness and stagnation lung syndrome or dampness and heat-accumulation lung syndrome), moderate subperiod (cold dampness lung syndrome or dampness and stagnation lung syndrome), severe subperiod (plague poison and lung-closing syndrome or syndrome of flaring heat in qifen and yingfen), critical subperiod (syndrome of inner blocking causing collapse), and convalescent subperiod (lung and spleen qi deficiency syndrome or Qi and Yin deficiency syndrome)[14]. There were several TCM injections newly included for the treatment of COVID-19 patients, which improved the selectivity and precision of medication use. Three more TCM injections, Reduning injection, Tanreqing injection, and Xingnaojing injection, were recommended in the severe subperiod and four more TCM injections, Reduning injection, Tanreqing injection, Xingnaojing injection, and Shenmai injection, were recommended in the critical subperiod.

No changes in the recommendations of use and types of TCMs for the treatment of COVID-19 were made in the 7th version protocol.

Western Medicine Recommendations for COVID-19

At the beginning of the COVID-19 outbreak, no specific western drug with robust evidence was available. The new use of old drugs and the combined use of existing broad-spectrum antiviral drugs have constituted the most effective and efficient methods to combat COVID-19. INF-α inhalation and oral Lopinavir/Ritonavir were the only 2 antiviral therapies recommended in the 3rd version the Diagnosis and Treatment Protocol for COVID-19 [10]. Ribavirin was then recommended in the 5th version of the protocol, considering its clinical benefits in the treatment of Severe Acute Respiratory Syndrome (SARS)[32]. Umifenovir was included in the 6th protocol version, on the basis of in-vitro cell experiments showing effective inhibition of SARS-CoV-2 infection [33]. The large-scale spread of the epidemic has made the quick accumulation of treatment experience possible, as well as open clinical trials allowing for the treatment protocol to be updated and to offer more detailed and practical information regarding the eligibility of patients, antivirus drug dosages, and the observation of adverse events.

Of all the antivirus targeted drugs recommended in the protocol, Chloroquine appears to have the potential to emerge as the standard choice due to promising preclinical evidence [34-36], preliminary clinical results and clinical experience unpublished (Ref). Thus far, 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 [37]. For example, COVID-19 patients treated with antiviral drugs, Lopinavir/Ritonavir and Umifenovir, showed negative nucleic acid detection on an average of 6 to 7 days of treatment, while the average time for Chloroquine Phosphate treatment to show negative nucleic acid detection was 4.2 days [38]. However, another well conducted study has shown no benefit of Lopinavir/Ritonavir (Ref). Despite the limited clinical evidence, experts from health regulation authorities and clinical trial organizers generally supported Chloroquine Phosphate as having a potent impact against SARS-CoV-2. This contributed to the inclusion of Chloroquine Phosphate in the 6th protocol version [14]. As Chloroquine emerged as the preferred treatment option, the recommendations related to the dosage regimen of Chloroquine for treatment of COVID-19 were updated and improved along with the accumulation of research evidence and knowledge on disease progression for COVID-19.

Several guidelines (**Error! Reference source not found.**) published in China supported the used of Chloroquine Phosphate for the treatment of COVID-19. The dosage of 500mg Chloroquine Phosphate, twice per day, and for a duration no longer than 10 days was first proposed for the treatment of COVID-19 in the 6th protocol version[14]. The Health Commission of Guangdong Province supported this recommendation, but outlined the importance of monitoring adverse events associated with the Chloroquine Phosphate, such as the risk of prolongation of Q-T interval when combined with macrolide antibiotics (e.g., azithromycin) [39]. Afterwards, the Health Commission of Hubei Province warned that Chloroquine Phosphate could cause the occurrence of sudden death at a dosage of 2~4g [30]. With the emergence of the safety issues mentioned above, the National Health Commission adjusted the dosage of Chloroquine Phosphate for adults by taking into consideration a patient's age and body weight.

Additionally, the contraindications for the use of Chloroquine Phosphate were also specified, such as in patients with underlying cardiovascular diseases [31]. The new dosage adjustment of the Chloroquine Phosphate was included in the 7th version of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [15] and the Guangdong expert consensus [22].

Hydroxychloroquine shares similar chemical structures and mechanisms of action with Chloroquine Phosphate, thus it is less surprising that Hydroxychloroquine may also be a candidate to combat the SARS-CoV-2 infection. Encouraging results proved that Hydroxychloroquine also had an in-vitro impact against SARS-CoV-2 [35, 36]. On February 15th, 2020, the website of People's Hospital of Wuhan University released a report titled "Hydroxychloroquine showed short-term efficacy in the treatment of Novel Coronavirus Pneumonia" [40]. In this report, researchers found that none of the 80 patients with systemic lupus erythematosus treated in the hospital's dermatology department were infected by COVID-19 during the period of SARS-CoV-2 transmission in Wuhan. The researchers suspected that Hydroxychloroquine might hold promises to protect the patients from COVID-19. Therefore, Hydroxychloroquine was recommended for the first time in the Shanghai expert consensus for COVID-19 [21]. The Shandong expert consensus specified the dosage of Hydroxychloroquine as 200mg, three times per day [23].

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4. Discussion

It is evident that China has taken the development of guidelines for the treatment of COVID-19 very seriously with the available guidelines targeting multiple topics and aspects relating to SARS-CoV-2. Interestingly, these guidelines have provided support for most of the issues healthcare professionals and hospital managers may face. Most of the guidelines were developed at the national level, with most of the regional guidelines in line with national guidelines, yet also customized to regions and providing more detailed instructions – with the exception of Shanghai, where guidelines tend to deviate from national guidelines and where, ultimately, the guidelines focused on hydroxychloroquine. China is traditionally highly centralized and, at the same time, its decentralized model has proven to be effective in such an outbreak. The development of guidelines has been a very dynamic process with very fast and continuous updating of existing guidelines. Although the guidelines provide limited information on the rational for their updates, it is considered that they were updated based on the development of clinical experience in treating patients and the evidence emerging from the large range of ongoing open studies.

Twenty-three guidelines have been targeting the pharmacological management of COVID-19 patients. Initially, Interferon-α and Interferon-K (in Shanghai guideline only), were recommended. Lopinavir/Ritonavir combination was recommended in all guidelines, except in Shanghai. A randomized, controlled, open-label trial involving 199 hospitalized adult patients with severe Covid-19 could provide an answer for the exclusion of Lopinavir/Ritonavir combination in the Shanghai expert consensus, as no benefit was observed with lopinavir–ritonavir treatment beyond the standard of care[41]. Umifenovir was approved in Russia and China, but not approved in Europe and the US. Oseltamivir and Remdesivir, have been initially widely recommended for influenza and other viral diseases, but were recommended to a lesser extent as an antiviral therapy for COVID-19. It does not seem that these products have gained significant interest since. Tocilizumab was just recommended for severe cases in the latest 7th version of the Diagnosis and Treatment Protocol. TCMs were widely used, alone or in combination with other antivirus drugs, in several going clinical trials in China. However, the potential for use of TCMs outside of China remains very limited in the current crisis.

Overtime, Chloroquine Phosphate and Hydroxychloroquine have become the mainstream treatments recommended in the 5 most prominent guidelines in China [14, 15, 21-23](Table 3). Chloroquine Phosphate was recommended for the first time on the 19th of February 2020 and since then all new guidelines and updates of guidelines have recommended Chloroquine Phosphate in addition to other therapies. Although there were observable inconsistences in the recommendations of Chloroquine Phosphate or Hydroxychloroquine or both across different provinces, it could be assumed that the Chinese national treatment guidelines for COVID-19 were based on a certain amount of clinical evidence. In these guidelines, Chloroquine Phosphate and Hydroxychloroquine have appeared as one of the pillar therapies for COVID-19.

In virology, it is well established that in-vitro results are poorly predictive of clinical outcome even in the case of Chloroquine Phosphate and Hydroxychloroquine for treating a variety of viruses [42]. Researchers in Shanghai showed confidence that Hydroxychloroquine could be a potential choice to reverse this pandemic. This was due to the fact that the number of new severe and critical COVID-19 cases in Shanghai have decreased significantly since Hydroxychloroquine was used for the treatment of COVID-19 since the 5th of February 2020 [43]. The effectiveness of Hydroxychloroquine (combined with basic treatment) was studied in 20 patients with COVID-19 beginning on the 17th of February 2020. After treatment with Hydroxychloroquine, the clinical symptoms of these 20 patients were significantly improved in 1~2 days. Chen et al. conducted a randomized study including 62 patients to investigate the efficacy of Hydroxychloroquine, which suggested a significant shorter time to clinical recovery, temperature recovery, and cough remission in patients receiving Hydroxychloroquine compared with those in control group [44]. Gautret et al. also reported that Hydroxychloroquine alone or in combination with Azithromycin reduced the detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with the control group in an open label, non-randomized clinical trial [45] and showed a rapid decline in the detection of SARS-CoV-2 RNA in upper respiratory tract specimens and length of stay in highly contagious wards in his later

observational study including 80 patients [46]. However, one small pilot study including 30 patients investigating the standard dose of Hydroxychloroquine (400 mg, once per day) in the treatment of patients with COVID-19 did not show significant clinical benefits compared with the standard of care (other antiviral therapies) in the negative conversion rate of COVID-19 nucleic acid [47]. Several factors may explain these differences in the clinical results between the two studies. When patients are treated at an early stage of disease with a relatively lower risk of further progression, they will likely resolve the disease spontaneously, thus bringing the response rate very high and being unable to detect the differences between study groups. However, when patients are treated too late, the acute inflammation related to cytokines blast [48]will prevent treatments to reach their target and make the patients unresponsive to potentially effective drugs.

The effectiveness of Chloroquine Phosphate and Hydroxychloroquine still remains to be examined in rigorous, comparative studies before any firm conclusions may be drawn. Furthermore, the adverse effects of Chloroquine must be closely monitored to minimize its potential harms in already vulnerable COVID-19 patients.

However, in the current situation where a high risk of fatal outcome or hospitalization in the intensive care unit is obvious, it is important to consider a probabilistic outcome. As far as the authors' knowledge, Chloroquine and Hydroxychloroquine remain as the treatment options having a relatively high level of evidence. In an Evidence-Based Medicine grading system, these treatments will likely be scored a grade of 4 out of 5, which qualifies them to be issued conditional recommendations for use under close medical monitoring.

It remains unfortunate that more knowledge has not yet been shared at this point at the time of publication when the pandemic may severely target Africa. In Africa, the healthcare infrastructure will be unable to absorb the consequences of a pandemic that may affect up to one-third or more of the population. Physical distancing is unlikely feasible due to the extreme poverty and cultural standards and habits. People are living together in large numbers, with as many as 20 persons in a single large room. Houses in large cities and suburbs with different families are all built one next to the other, with no clear dividers distinguishing properties and where who lives exactly. It is also common, cultural practice that when someone gets sick, all their relatives and close friends visit to check on the ill person and to spend time with them, thus increasing contact with ill people. Most people live off of informal, noncontractual work. They are, therefore, paid every day and with these low wages they must manage to feed their family. A pandemic, such as COVID-19, may force people in such situations to choose between either respecting confinement and losing their jobs and daily wages, therefore being unable to feed their families, or they will leave home in order to work and disseminate the virus, overwhelming their ill-prepared healthcare system. In Africa, they are recommended to wash their hands frequently, yet a vast majority do not have access to water and even when they do, they must carry it by hand over long distances. Moreover, they have little access to soap and cleansing products. They are recommended to blow their nose in disposable handkerchiefs, which they cannot afford, and are recommended to sneeze in their elbows, while in this season will find many dressed in short sleeves. It is apparent that without an effective, affordable pharmaceutical, such as Hydroxychloroquine or Chloroquine Phosphate, or any other potentially effective product, a pandemic disaster is bound to impact Africa.

Many of the obstacles faced by Africa are currently being seen in India as well. The 21-day nationwide lockdown plan implemented by Prime Minister Narendra Modi's, might only work for India's middle and upper classes, who have less difficulties to meet their basic life needs and who may even work from home, using modern technology. However, social distancing is impractical for the approximate 74 million people living in the country's slums, which are known for their extreme poverty, unsanitary conditions, and inaccessibility to bathrooms and clean water [49]. As of the 1st of April 2020, India has recorded 1466 COVID-19 cases and 38 deaths [50]. The actual number of patients affected by COVID-19 in India could be underestimated due to their limited detection capacity. It is concerning that a catastrophe will occur in this country, home to the world's second largest population. Other developing countries generally share the common features and face the same threats as those in India. The lack of clear WHO recommendations for using this ammunition considered by the Chinese as one of the ultimate options to control the pandemic may have long-term consequences on the WHO's credibility in developing countries.

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WHO currently has provided guidance that is inapplicable and has stated that it awaits more robust evidence before supporting Chloroquine Phosphate for the treatment of COVID-19.

5. Conclusion

China has generated and continues to generate a massive source of information with several guidelines addressing almost all aspects of COVID-19 management. Guidelines were mainly from the central government and national associations, however, customization of guidelines was also allowed at the regional level. Only the Shanghai province deviated from central government guidelines, with Hydroxychloroquine and Chloroquine Phosphate being the most preferred treatments. These guidelines were likely based on evidence that is critical for defeating the COVID-19 pandemic. It would be of significant importance that Chinese scientists could share their valuable knowledge and insight on COVID-19 timely with global scientific communities. To date, all the evidence and decisions in China point towards Hydroxychloroquine and Chloroquine Phosphate as the effective therapies for COVID-19, despite some clinical evidence yet to be disclosed

WHO seems to not be giving enough consideration to the extensive knowledge to be gained from Chinese researchers. Instead, they have proposed recommendations inapplicable around most of the world and have hesitated to endorse the use of Chloroquine Phosphate, which has seemed to be the best option so far, despite the limited knowledge available. Most developing countries have developed guidelines to use Chloroquine or Hydroxychloroquine for the treatment of COVID-19, thus, distancing from WHO's recommendations. If clinical trials currently conducted in the western world finally prove Chloroquine Phosphate or Hydroxychloroquine to be an effective treatment option, WHO may damage the little credibility remaining that they have after the mismanagement of several previous outbreaks [51]. As the pandemic continues to unfold, additional clinical evidence for the treatment of COVID-19 will continue to emerge from China as well as other countries.

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CONFLICT OF INTEREST

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Table 1 Chinese Guidelines for the pharmacological treatment of COVID-19

Type	Title	Publish Date	TCM	IFN-α	IFN-k	Lopinavir /Ritonavir	Ribavirin	Chloroquine	Hydroxy-chloroquine	Umifenovir	Other antivirus drugs	Tocilizumab
National guideline	Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (3rd version) [10]	2020-01-23	Yes	Yes	No	Yes	No	No	No	No	No	No
	Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (4th version) [11]	2020-01-27	Yes	Yes	No	Yes	No	No	No	No	No	No
	Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5thversion) [12]	2020-02-05	Yes	Yes	No	Yes	Yes	No	No	No	No	No
	Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th version updated) [13]	2020-02-08	Yes	Yes	No	Yes	Yes	No	No	No	No	No
	Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th version) [14]	2020-02-19	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No
	Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (7th version) [15]	2020-03-04	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes
Rapid advice guideline	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (1st Edition) [17]	2020-01-22	Yes	Yes	No	Yes	No	No	No	Yes	Oseltamivir	No
	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (2nd Edition) [18]	2020-01-24	Yes	Yes	No	Yes	No	No	No	Yes	Oseltamivir	No
	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (3rd Edition) [16]	2020-01-28	Yes	Yes	No	Yes	No	No	No	Yes	Oseltamivir	No
	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version) [19]	2020-01-30	Yes	Yes	No	Yes	No	No	No	No	No	No
	A rapid advice guideline for diagnosis and treatment of COVID-19 (integrated version) [20]	2020-02-01	Yes	Yes	No	Yes	Yes	No	No	No	Remdesivir	No

COVID: Coronavirus Disease; IFN: Interferons; NA: Not applicable; TCM: Traditional Chinese Medicine

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Refer to Table 1 (continued)

Type	Title	Publish time	TCM	IFN-α	IFN-k	Lopinavir /Ritonavir	Ribavirin	Chloroquine	Hydroxy-chloroquine	Umifenovir	Other antivirus drugs	Tocilizumab
Province guidelines	Peking Union Medical College Hospital's proposal for diagnosis and treatment of "novel coronavirus-infected pneumonia" (V2.0) [24]	2020-01-30	Yes	No	No	Yes	No	No	No	No	No	No
	Shandong expert consensus on the diagnosis and treatment for COVID-19 [23]	2020-02-20	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No
	Shanghai expert consensus on the integrated treatment for novel coronavirus pneumonia [21]	2020-02-20	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No
	Guangdong province: Expert consensus on Chinese integrative medicine for Epidemic prevention and control of COVID-19 [22]	2020-03-10	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes
TCM	Shanghai: Protocol for the use of traditional Chinese medicine for the diagnosis and treatment of COVID-19 [25]	2020-02-24	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Beijing: Pharmacy Expert consensus for TCM Treatment of COVID-19 [27]	2020-02-28	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Hubei province: Protocol on the use of traditional Chinese medicine for Epidemic prevention and control of COVID-19 [28]	2020-02-29	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Expert consensus for appropriate application of TCM for COVID-19 [26]	2020-03-01	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Shanxi province: Protocol for the use of traditional Chinese medicine of COVID-19 [29]	2020-03-01	Yes	No	No	No	No	No	No	No	No	No
Chloroquine phosphate for COVID-19	Close monitoring the adverse effects of chloroquine phosphate for the treatment of novel coronavirus pneumonia[30]	2020-02-21	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA
	Notifications on the adjustment of dosage of chloroquine phosphate for the treatment of novel coronavirus pneumonia[31]	2020-02-28	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA
	Guangdong province: Expert consensus on chloroquine phosphate for COVID-19 [39]	2020-03-04	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA

COVID: Coronavirus Disease; IFN: Interferons; NA: Not applicable; TCM: Traditional Chinese Medicine

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Table 2 Summary of TCMs in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia

Protocol Version	Publish date	Basis of TCM Recommendation	TCM injection Recommendations
3rd [10]	2020-01-22	Recommendations for different prescriptions according to the different symptoms (dampness, heat, poison and stasis) of the lung	No recommendation
4th [11]	2020-01-27	Recommendations for different prescriptions according to the medical observation period, clinical treatment period (mild, moderate, severe, convalescent period)	Moderate period: Xiyanping injection and Xuebijing injection Severe period: Xuebijing injection, Shenfu injection and Shengmai injection
5th [13]	2020-02-05	No changes implemented since previous version	No changes implemented since previous version
5th revised [12]	2020-02-08		
6th [14]	2020-02-18	General prescriptions are added during the clinical treatment period; The clinical treatment period is divided into 5 subperiods mild, moderate, severe, critical, and convalescent; Different prescriptions are recommended according to different symptoms of different subperiods	Severe cases: Xiyanping injection, Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection. Critical cases: Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection, Shenfu injection, Shengmai injection, Shenmai injection.
7th [15]	2020-03-04	No changes implemented since previous version	No changes implemented since previous version

TCM: Traditional Chinese Medicine

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Table 3 The inclusion of Chloroquine Phosphate and Hydroxychloroquine Sulphate in guidelines for the treatment of COVID-19

Publish date	Guideline name	Publishing organization	Key information related to chloroquine and Hydroxychloroquine
2020-02-18	The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th version)[14]	National Health Commission	Eligibility: general treatments for all COVID-19 cases, regardless of disease severity. Dosage: 500 mg bid, use no longer than 10 days.
2020-02-20	Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia[39]	Health Commission of Guangdong Province for chloroquine in the COVID-19 treatment	It recommended chloroquine phosphate tablet, 500 mg bid for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine. Contraindicated to use combined with macrolide antibiotics including azithromycin.
2020-02-21	Close monitoring the adverse effects of chloroquine phosphate for the treatment of novel coronavirus pneumonia[30]	Health Commission of Hubei Province	Chloroquine phosphate can cause acute death. Lethal dose for adults is 2-4 g.
2020-02-28	Notifications on the adjustment of dosage of chloroquine phosphate for the treatment of novel coronavirus pneumonia[31]	National Health Commission	Chloroquine phosphate (500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1-2 and 500 mg qd. for Days 3-7 for adults with body weight below 50 kg) Contraindicated to use combined with macrolide antibiotics including azithromycin.
2020-03-02	Shanghai expert consensus on the integrated treatment for novel coronavirus pneumonia[21]	Shanghai expert panel on the clinical treatments for COVID-19	Hydroxychloroquine Sulphate and Chloroquine phosphate were both recommended.
2020-03-04	The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (7th version)[15]	National Health Commission	Chloroquine phosphate (500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1-2 and 500 mg qd. for Days 3-7 for adults with body weight below 50 kg)
2020-03-05	Guangdong expert consensus on the Chinese integrative medicines for the prevention and treatment of COVID-19[22]	Guangdong association of integrative medicine	Chloroquine phosphate (500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1-2 and 500 mg qd. for Days 3-7 for adults with body weight below 50 kg)
2020-03-15	Shandong expert consensus on the Diagnosis and Treatment for Novel Coronavirus Pneumonia[23]	Shandong expert panel on the clinical treatments for COVID-19	Hydroxychloroquine Sulphate (200 mg tid).

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Figure 1 Cumulative number of the included guidelines related to COVID-19

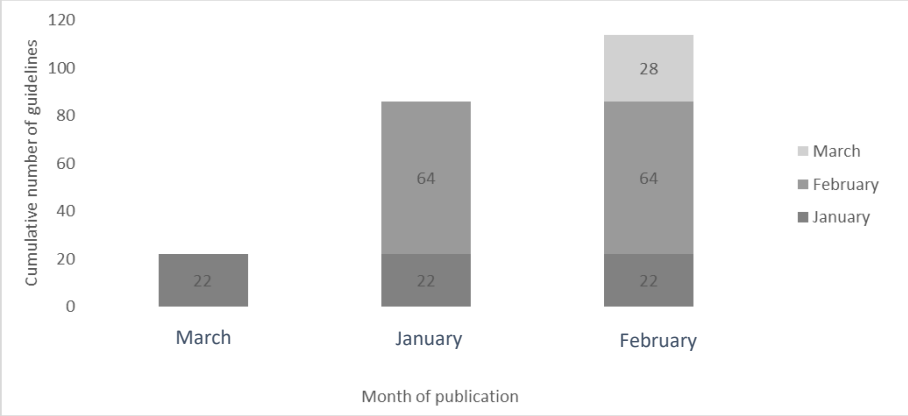

Figure 2 Source of guidelines related to COVID-19 in China

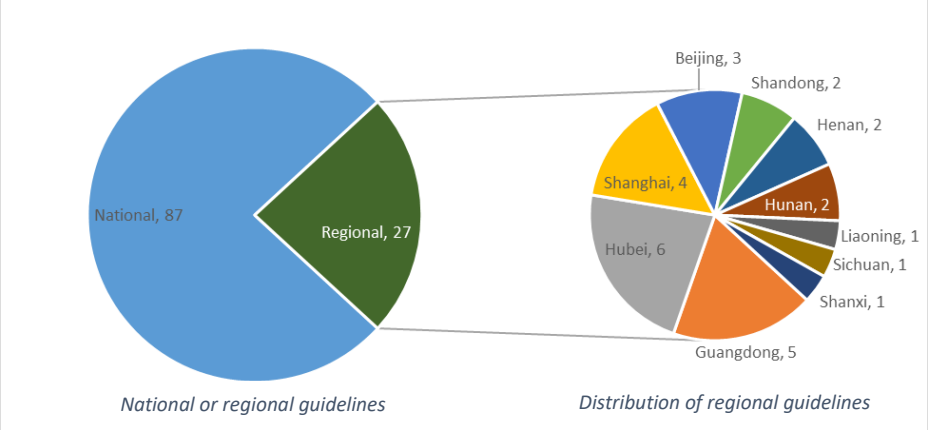

Figure 3 Objective of included guidelines related to COVID-19

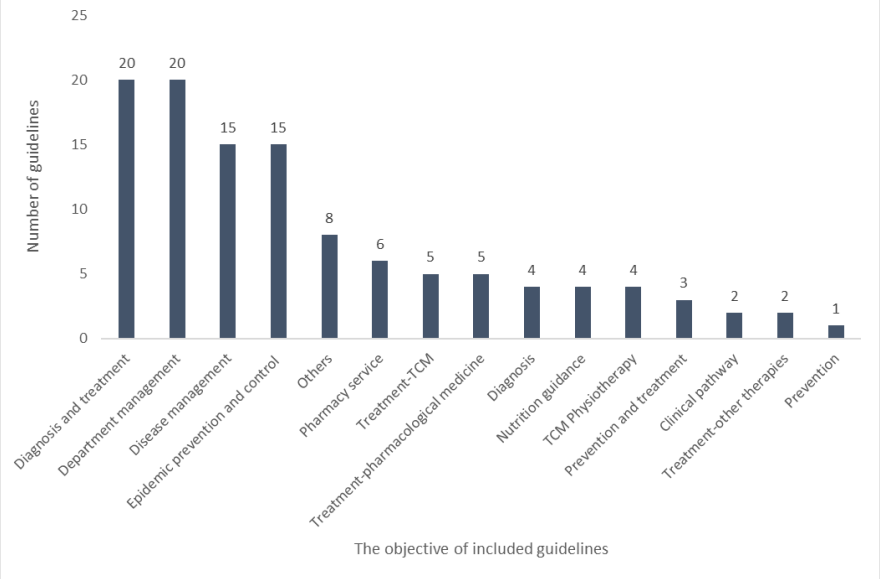

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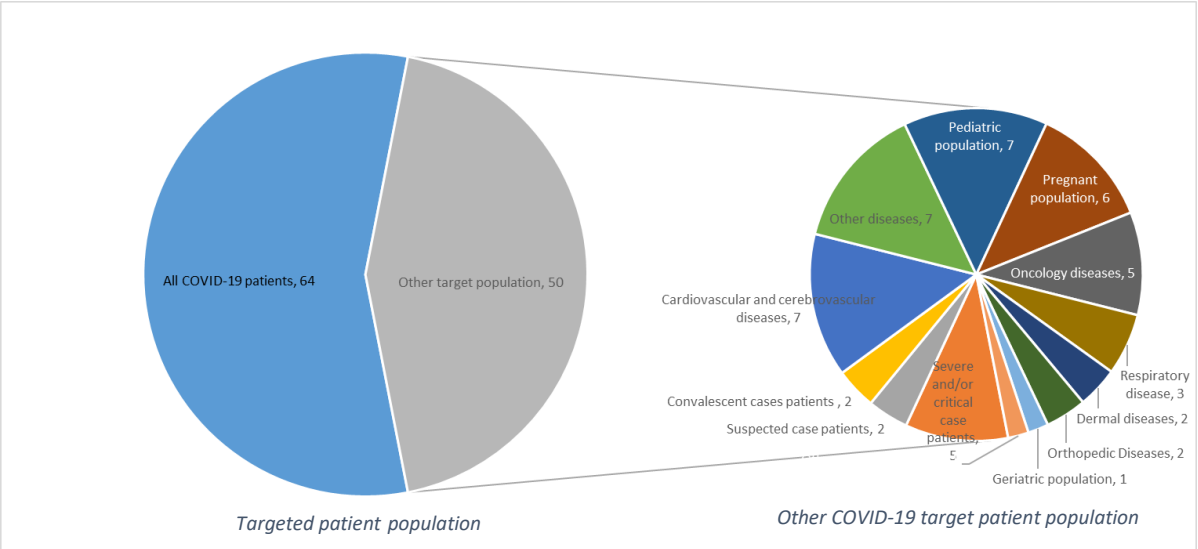
Figure 4 Target patient populations of included guidelines related to COVID-19



Targeted patient population

Other COVID-19 target patient population