Original Article

The Analysis of Global COVID-19 Clinical Trials Registries

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Background: Corona Virus Disease 2019 (COVID-19) is a pandemic-associated health emergency. Multiple preventive strategies have been implemented to try to prevent its transmission, and no drugs have proven to be highly effective yet. There are many ongoing clinical studies of COVID-19 and the information is scattered in each country's own database.

Objective: To provide the insight of the ongoing COVID-19 studies and present the database information to researchers. Healthcare provider can follow these COVID-19 studies and prepare for the upcoming second wave.

Materials and Methods: The authors' searched all COVID-19 studies that were listed in clinical trial registries worldwide and extracted information from each study. The authors' reported these studies including study population, type of study, country of origin, treatment assigned in controlled clinical trials, and matched the date of registration to the real-world cases.

Results: Two thousand nine hundred forty-nine studies from 18 registries were found. Over 2,000 (2,224) studies (75.4%) targeted symptomatic COVID-19 patients, 387 studies (13.1%) targeted non-infected general population, and 237 studies (8.1%) included healthcare personnel. Clinical controlled trials were found in 1,491 studies (50.6%) and 1,346 studies (45.6%) were observational studies. ClinicalTrials.gov was the most prevalent registry, followed by Chinese Clinical Trial Registry (ChiCTR). China also had the highest number of registered trials. Antimalarials and antivirals were the most frequently used treatments in the controlled trials. The number of trials registered increased in parallel to the total number of real-world cases.

Conclusion: The number of ongoing COVID-19 clinical trials are steadily increasing. The present study provides an overview of registered studies from worldwide databases, which researchers can use to plan and conduct future studies.

Keywords: COVID-19, Clinical trial registry, Global trend

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Corona Virus Disease 2019 (COVID-19) is an ongoing pandemic that causes high mortality, especially in elderly patients and patients with underlying medical comorbidities[1-3]. At the end of May 2020, 5,371,158 patients were infected and 342,894 deaths globally were reported, (https://covid19.who.int/). The emerging pathogen has been newly identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can cause pneumonia in the same way as in previous outbreaks of severe acute respiratory syndrome (SARS) caused by SARS-CoV in 2002 and Middle East respiratory syndrome (MERS) caused by MERS-CoV in 2012[4-6]. Although, case fatality rate of COVID-19 is less than SARS and MERS[1,7], asymptomatic patients who are infected with SARS-CoV-2 can effectively spread the pathogen by respiratory droplets[7,8]. In contrast, SARS-CoV and MERS-CoV viral shedding is found only after symptom onset, which usually occurs in the hospital or in a few family members[5,9,10]. Thus, the human-to-human transmission of SARS-CoV-2 occurs widely in communities and results in higher reproductive number (R_0 around 2 to 2.5) compared with SARS-CoV and MERS-CoV (R_0 around 1.7 to 1.9 and 0.7, respectively), which leads to more COVID-19 patients than from SARS and MERS (8,096 and 858 global cases, respectively)[1,5,7,11,12].

Although COVID-19 in countries such as China, Thailand, South Korea, and Taiwan had early outbreaks that are now constrained[13], many countries

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are still suffering from uncontrolled outbreaks and local transmission, resulting in an increase in new cases and patient deaths. Many medical centers are establishing COVID-19 clinical studies to combat the virus[11,14,15]. These studies cover all the aspects of COVID-19, including treatment, natural history of the disease, long-term outcomes, immunity in convalescent patients, prevention of transmission, and vaccine development. For non-infected populations, which include family members of the patients, close-contact personnel, and healthcare workers, they are being studied not only from the aspect of transmission prevention, but also with respect to the mental health and psychoanalytical impact of COVID-19[16,17]. These clinical studies emphasize the physical and mental global-scale effects of COVID-19. However, information about clinical trials is scattered throughout the registry databases and might confuse researchers who would like to follow this information.

In the present study, the authors collected all data from worldwide clinical trial registries, which can also be obtained from the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP at www.who.in/icrp/en/). The authors analyzed the data that included study populations, study designs, and interventions assigned to patients or non-infected populations, and then compared the number of registered trials with the total number of cases in a particular country to estimate the effects of COVID-19 on research development.

Materials and Methods

Studies of COVID-19 registered in the national registries up to May 29, 2020 were included to the present analysis. This date limitation was because the authors expected to see the result after each study was conducted for at least six months. The registries were listed alphabetically as followed: Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBEC), Chinese Clinical Trial Registry (ChiCTR), Clinical Research Information Service (CRiS) - Republic of Korea, ClinicalTrials.gov, Clinical Trials Registry - India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), European Union Clinical Trials Register (EU-CTR), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), International Standard Randomized Controlled Trial Number (ISRCTN), Japan Primary Registries Network (JPRN), Lebanese Clinical Trials Registry (LBCTR), Pan African Clinical Trial Registry (PACTR), Peruvian Clinical Trial Registry (REPEC), Thai Clinical Trials Registry (TCTR), The Netherlands National Trial Register (NTR), and Sri Lanka Clinical Trials Registry (SLCTR). Clinical trials and studies in each registry can be found on the registry's websites and in the WHO-ICTRP (www.who.in/icrp/en/) that included every registry in a single searchable portal database.

The authors performed the analyses of studies registered in the database mentioned above, and extracted data from each clinical trial, including scientific title, date of registration, source of registry database, countries that performed study, inclusion gender and age, target population, study design, intervention and control groups, and subspecialty specificity. Cancelled and non-COVID-19-related studies were excluded from the analyses. Duplicated studies among different registries were identified and excluded based on the scientific titles, target populations, assigned interventions, affiliations, and date of registration. The authors then compared the number of registered trials per date with the real-world data of COVID-19 new cases on that date, which can be found at https://ourworldindata.org/coronavirus-source-data. This dataset is an open-source, free-to-use for all purposes, is updated daily, and includes data on confirmed cases, deaths, and testing.

Results were reported as numbers with percentages and were illustrated in bar charts and maps. Crude total cases, total cases per million, and number of trials registered were demonstrated using a bubble scatter chart. All data were analyzed in Stata Statistical Software, version 15.1 (StataCorp LLC, College Station, TX, USA).

The present study was not directly involved in human or animal. The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, had exempted the present study (IRB No. 509/63) in compliance with the International Guidelines for Human Research Protection as Declaration of Helsinki, the Belmont Report, CIOMS Guideline, International Conference on Harmonization in Good Clinical Practice (ICH-GCP), and 45CFR 46.101(b).

Results

Study characteristics are displayed in Table 1. The authors found 2,949 registered studies in all databases. Symptomatic COVID-19 patients were included in 2,224 studies (75.4%), 21 studies (0.7%) involved with asymptomatic patients, and 80 studies (2.7%) explored the recovered patients in convalescent phase of COVID-19. Non-infected

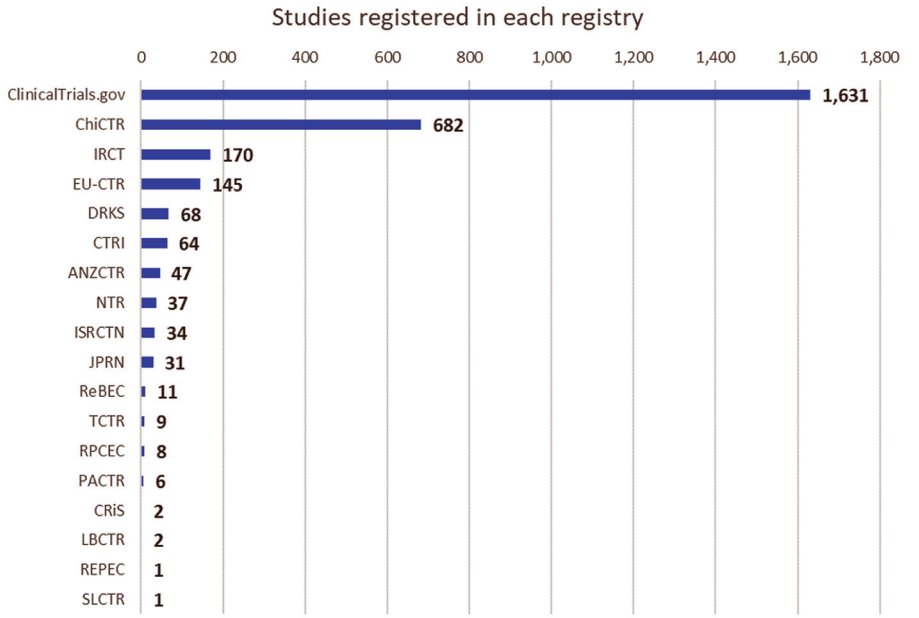

Figure 1. Studies registered in each registry.

ANZCTR=Australian New Zealand Clinical Trials Registry, ReBEC=Brazilian Clinical Trials Registry, ChiCTR=Chinese Clinical Trial Registry, CRiS=Clinical Research Information Service - Republic of Korea, CTRI=Clinical Trials Registry - India, RPCEC=Cuban Public Registry of Clinical Trials, EU-CTR=European Union Clinical Trials Register, DRKS=German Clinical Trials Register, IRCT=Iranian Registry of Clinical Trials, ISRCTN=International Standard Randomised Controlled Trial Number, JPRN=Japan Primary Registries Network, LBCTR=Lebanese Clinical Trials Registry, PACTR=Pan African Clinical Trial Registry, REPEC=Peruvian Clinical Trial Registry, TCTR=Thai Clinical Trials Registry, NTR=The Netherlands National Trial Register, SLCTR=Sri Lanka Clinical Trials Registry

Table 1. Characteristics of registered clinical studies

Variable	Number of studies; n (%)
Total registered studies	2,949
Population included	
Symptomatic patients	2,224 (75.4)
Asymptomatic patients	21 (0.7)
Recovered patients	80 (2.7)
Non-infected population	387 (13.1)
Healthcare personnel	237 (8.1)
Type of study	
Clinical trials with controlled group	1,491 (50.6)
Observational studies	1,346 (45.6)
Diagnostic studies	110 (3.7)
Meta-analysis	2 (0.1)
Study involved with pediatric patients	58 (2.0)

populations were also the primary target in 387 studies (13.1%). Healthcare personnel were included in 237 studies (7.9%).

For type of the present study, 1,491 (50.6%) were clinical trials with control groups with or without randomization. Observational studies were conducted in 1,346 studies (45.6%), and 110 studies (3.7%) involved diagnostic studies to evaluate the performance of different COVID-19 tests. Two studies (0.1%) were recorded as meta-analyses. Most studies targeted adults older than 18 years old. Only 58 studies (2.0%) primarily targeted pediatric patients.

Most studies were registered in ClinicalTrials.gov (1,631 studies, 55.3%), followed by ChiCTR (682 studies, 23.1%), IRCT (170 studies, 5.8%), and EU-CTR (145 studies, 4.9%). Complete details from each registry are shown in Figure 1. Eighty-four collaborating multi-countries studies that included patients with different nationalities and ethnicities were found. For the top five countries that had conducted studies involved with a single nationality, 781 studies were conducted in China followed by 315 studies in United States, 262 studies in France, 185 studies in Iran, and 118 studies in Spain. The number of studies registered in each country are illustrated in Figure 2.

Figure 3 shows the assigned treatments in clinical trials with control groups. Antimalarial drugs were assigned in 167 studies, and antiviral agents were allocated in 150 studies. One-hundred thirty-one studies studied traditional medicine, which were mostly Chinese herbs. Monoclonal antibodies (mostly

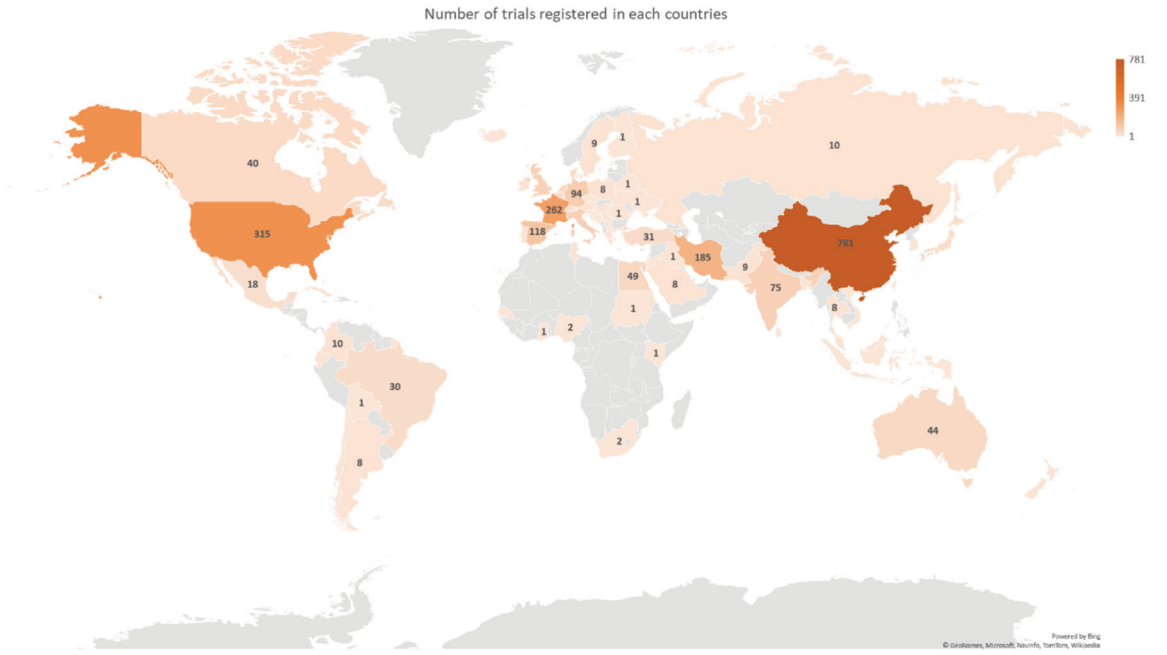

Figure 2. Number of trials registered in each country, excluding 84 multi-countries collaborative studies.

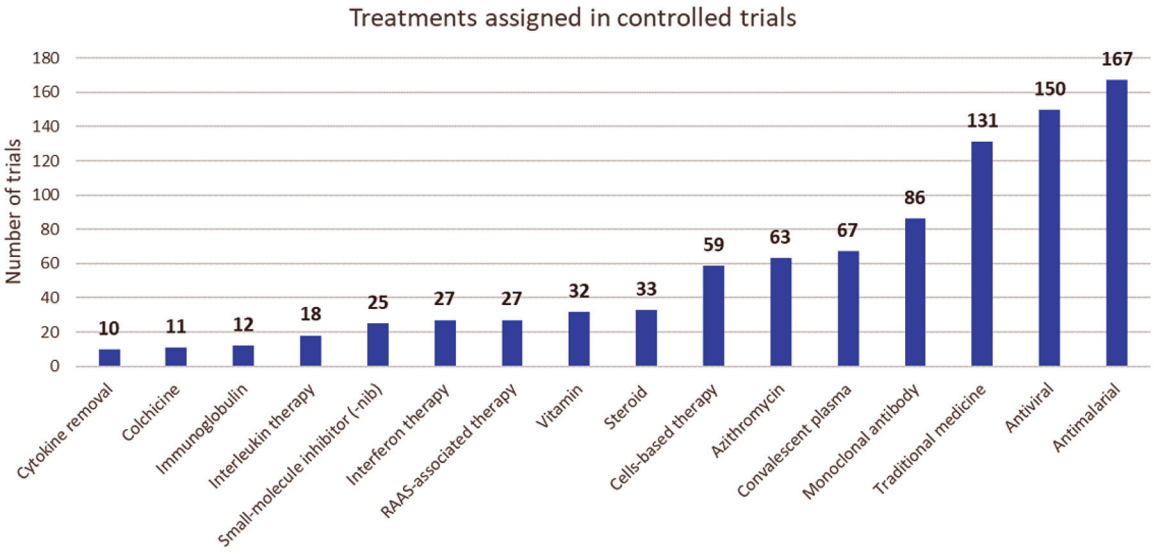

Figure 3. Treatments assigned in controlled trials.

anti-IL-6 receptor [Tocilizumab]), were included in 86 studies. Sixty-seven studies explored the potential effect of convalescent plasma from recovered patients for use in treating other ill patients. When the authors excluded COVID-19 studies from in the aspect of infectious disease or pulmonary medicine or critical care, which was found in almost every COVID-19 patient, the authors found 220 studies involved with the psychiatric aspect in infected and non-infected populations. For internal medicine subspecialties, cardiological events were investigated in 75 studies, followed by hematological aspects in 56 studies, and oncological patients in 48 studies. Complete details of each subspecialty can be found in Figure 4.

Figure 5 represents the correlation between total cases, total cases per million population, and volume

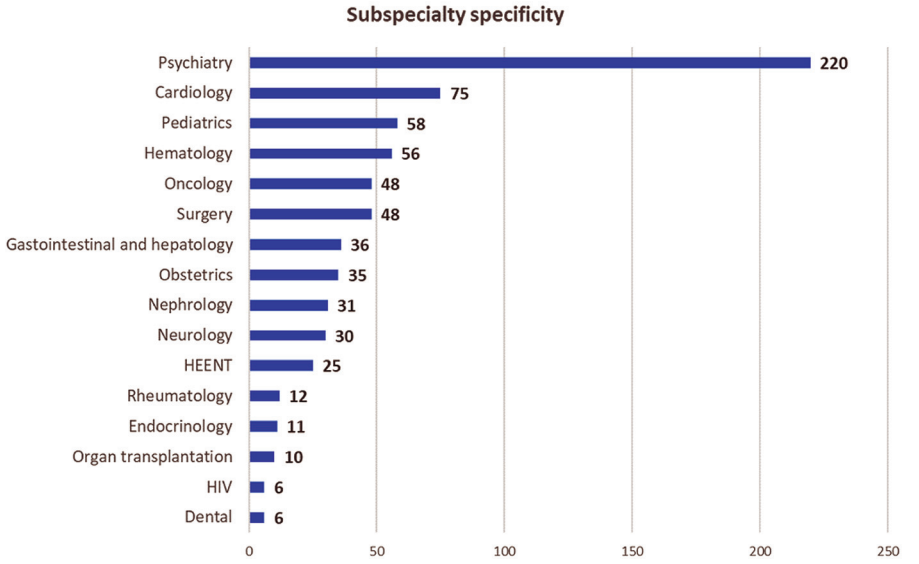

Figure 4. Number of studies that are specific for subspecialties, excluding infectious disease/pulmonary medicine/critical care aspects.

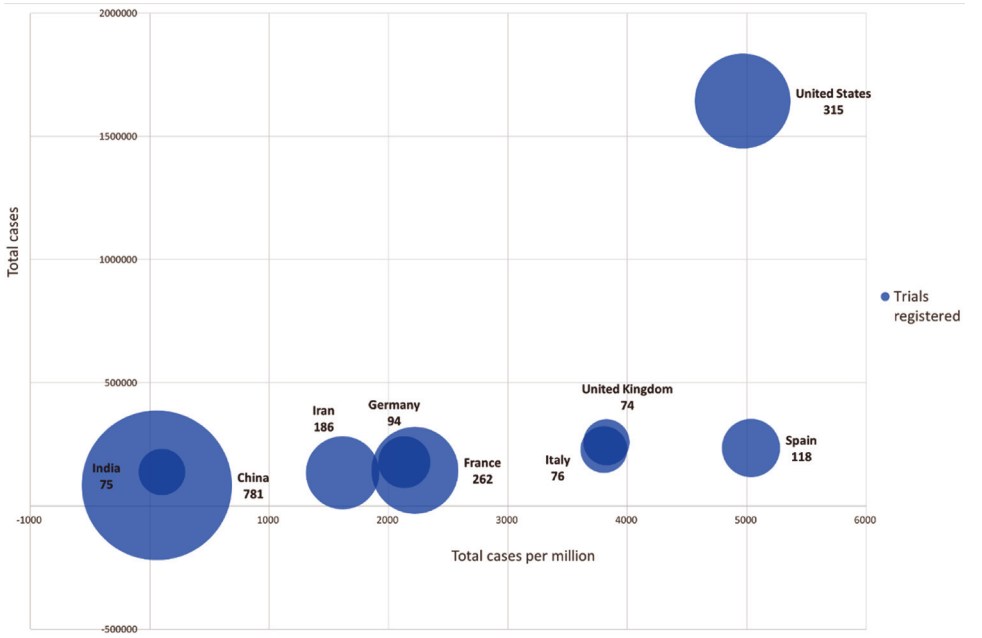

Figure 5. Correlation between total cases in each country, total cases per million population, and volume of registered trials in that country (excluding 84 multi-countries collaborative studies). Circle size and number represent volume of registered trials.

of trials that are registered in each country. The United States had the highest total cases as of May while Spain had the highest total cases per million. To date, China has the highest number of registered studies to total cases ratio (9.3 studies per thousand cases), followed by France (1.8 studies per thousand cases) and Iran (1.4 studies per thousand cases).

The authors compared the number of cumulative clinical trials registered in the database with world total cases and the present study data is presented in Figure 6. The number of trials started to rise at the beginning of February 2020 just after WHO declared this outbreak a Public Health Emergency of International Concern (PHEIC) on January 30, 2020[5]. The number of cases has been increasing since mid-March 2020 while many European countries

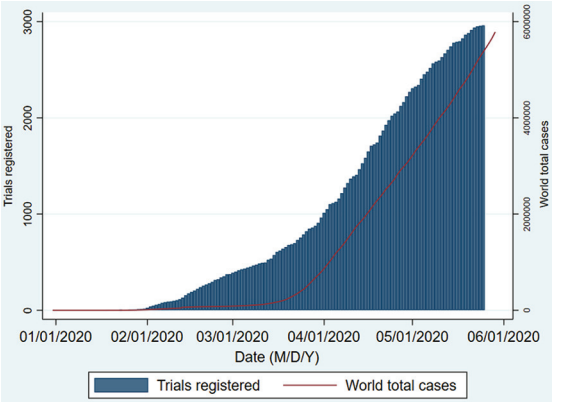

Figure 6. Cumulative clinical trials registered in the database compared with cumulative total worldwide cases.

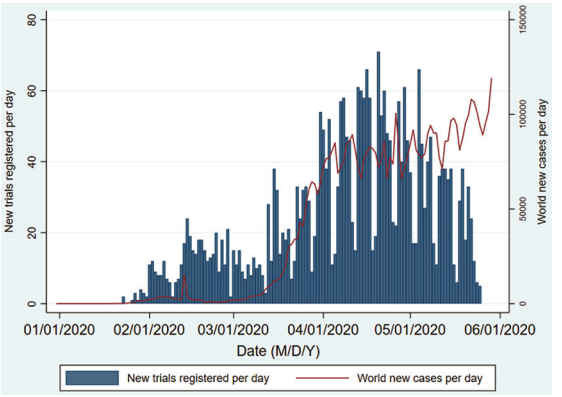

Figure 7. New clinical trials registered in the database per day compared with new worldwide cases per day.

started lockdowns[2,18,19]. The number of new clinical trials peaked in mid-April 2020, but the number of new cases has not yet reached its peak (Figure 7). The number of trials registered in each month was as followed, 29 trials in January, 363 trials in February, 594 trials in March, 1,324 trials in April, and 697 trials in May

Discussion

The authors examined the database of worldwide clinical trial registries during the COVID-19 pandemic. Most studies were controlled clinical trials that evaluated treatment regimens in symptomatic patients, with antimalarials and antivirals as the most frequently assigned treatment agents. ClinicalTrials.gov was the most utilized source of registration, while China was the country with the highest number of clinical trials and the clinical trials to total cases ratio. The present analyses demonstrated the correlation between the cumulative number of trials and the number of cumulative cases, which increased sharply in parallel.

COVID-19 is an international health menace in the form of an ongoing pandemic in 2020. Although the case fatality rate of COVID-19 is much lower than other recent pandemics such as MERS, SARS, and Ebola, the high infectivity rate of COVID-19 remains a major concern and results in the highest total death-related pandemic in the twenty-first century[20-22]. The very high number of COVID-19 patients requiring hospitalization also affects patients with other diseases. In countries with uncontrolled local transmission, COVID-19 patients overwhelm the healthcare resources and hospital beds and can push all other patients to receive less appropriate care[23-26]. Many strategies are being implemented for controlling virus transmission to try to "flatten the graph" of infected cases by providing enough time and resources for the healthcare system capacities to operate efficiently[27]. Some studies suggest that the interventions, including handwashing, physical distancing, wearing a mask, travel restriction, and searching for the sources and containment, can stop the spread of the virus[28-37]. In the present study, these are 21% of the registered trials focused on the non-infected populations and healthcare personnel. These studies were mainly involved with transmission prevention, psychological aspects, and vaccine development. In a middle of the health crisis as being now, the results of these studies should be closely followed and confirmed.

At the present time, no medications licensed for treatment of the SARS-CoV-2 currently exist. The authors found 75.4% of studies were involved with symptomatic COVID-19 patients, both consisting of clinical trials with control groups and observational studies. This provides a great opportunity for researchers to collaborate and work together to achieve high standard scientific outputs. However, the situation could be a double-edge sword. As many journals are recruiting COVID-19 publications to inform the clinicians and fight the virus, many articles are rushed through the fast-track peer-review processes and might result in inaccurate information. In early June 2020, the largest multicenter observational study with 96,032 COVID-19 patients was published in The Lancet, in which the harmful effects of antimalarials as the treatment for COVID-19 were described. These agents caused a decrease in hospital survival and increase ventricular arrhythmias[38]. This statement significantly impacted other ongoing

randomized clinical trials of antimalarials due to safety concerns[39]. However, the study was retracted by the authors after being questioned for the trustworthiness of the primary data source, which came from the data-providing company and could not be accessed by both the authors themselves and the third-party reviewers[39]. The uncertainty of the same data-providing company also caused the retraction of another study published in The New England Journal of Medicine by the same group of authors[40]. Currently, the authors have gone back to the beginning. WHO-based International Solidarity Clinical Trial that randomly allocates patients to the standard of care (SOC) or to the SOC and one with remdesivir, hydroxychloroquine, lopinavir with ritonavir, or lopinavir with ritonavir plus interferon-ß, might be able to enlighten us as to whether there are any benefits from these medications[41]. It is worth noting that effective COVID-19 prevention protocols might lower the number of new cases and delay the recruitment rate in addition to enlarging the study's results.

The present study presented the updated data of COVID-19 clinical studies from the first half of the year 2020. The authors extracted all important data from every available registry to be used as fundamental knowledge for all researchers and for conducting further appropriate studies. With respect to the study limitations, the present study provided only trials registered to the end of May 2020, which the results can be expected after six months in the end of year 2020; however, researchers can search in the websites mentioned in the methods section for the real-time updated registries and total COVID-19 cases. Although the results in the present study are not updated in real-time, the authors have shown the rapid increasing rate of the registered studies as response to the pandemic in the current era of well-developed technology, as could be expected if there will be new emerging diseases in the future. In addition, there are some differences such as study designs and types that could confuse the readers about the termed used in each registry, among the input of each registry database. The authors would suggest, if possible, to combine all databases in the future, which would be run by the central organization such as WHO and would not depend on a single country. This method would facilitate searching by clinicians and researchers. Moreover, one should be aware that not every trial in the registries can be carried out completely, as some studies might be terminated early due to the difficulties in recruiting subjects or insufficient funding.

Conclusion

In conclusion, COVID-19 is an emerging pandemic that will stay with us for quite a while. Effective treatments and preventive strategies are not yet fulfilled. The present study could provide an overview of the ongoing trials and might help researchers to appropriately design further scientific studies for combatting COVID-19.

What is already known on this topic?

COVID-19 is an emerging pandemic and numerous studies are being carried all around the world. However, the information of these studies is scattered, and the overall picture is lacking.

What this study adds?

The authors collected all information of the current ongoing COVID-19 studies. Healthcare provider will be able to see the overview of these studies, which will also help conducting of new studies in the fields which are still insufficient.

Acknowledgement

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Conflicts of interest

Dr. Wasee Tulvatana is appointed by the Thai Clinical Trials Registry (TCTR) as part of the steering and administrative committee. Other authors declared no conflict of interests.

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