Visualization analysis of the characteristics of COVID-19 clinical trials

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Research

Keywords: COVID-19, Clinical trial, Antivirals, Primary endpoint, Data visualization

Posted Date: May 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-21472/v2

Abstract

Background As a highly contagious disease, COVID-19 is raging on and is faced by every human being. Clinical trials are one of the most important means of investigating treatments for COVID-19, and their effective implementations may address the massive spread of the pandemic. As clinical trials continue to be conducted, the inability to view large amounts of data at a glance becomes a problem for many researchers. In order to provide reference and assistance for clinical trial design, this study collected and analyzed the current COVID-19 clinical trial registration data from multiple sources, and subsequently discussed their research status and developmental trend.

Method The registered data of COVID-19 clinical trials were gathered from the ChiCTR and ClinicalTrials.gov website, which were transformed by Python and further demonstrated by Apache ECharts.

Results As of March 28, 2020, records of 677 eligible registered trials had been retrieved. Overall, there are 407 (60.12%) interventional studies and 270 (39.12%) observational studies; 522 (77.10%) trials were conducted by hospitals; 53.32% of trials would be completed within six months; 523 (77.25%) subjects in trials were confirmed cases. Among interventional studies, 70.27% of the trials were randomized parallel studies; 55 (13.51%) trials considered time condition for clinical recovery as the primary endpoint, and 46 (11.30%) trials through clinical parameters and laboratory index as the primary endpoint. In the selection of intervention measures, chemical or biological agents constituted 43.49%, of which antiviral ones accounted for 14.50%, and antimalarials accounted for 8.85%, and 98 (24.14%) cases of studies involving TCM or integrated medicine. In addition, this study further analyzed antiviral drugs and explored possibilities of using combined drugs. Although a large number of clinical trials are already underway, interim research data will be helpful for future trial design and drug selection.

Conclusions By compiling representative information of topical COVID-19 clinical trial registration, this study complements and enhances the effects of future researchers' trial designs.

Introduction

Since the outbreak of pneumonia cases caused by COVID-19 in December 2019, the pandemic spreads rapidly. Medical researchers and clinicians have immediately and wholeheartedly devoted their effort to discovering a potential treatment. On January 31, 2020, the World Health Organization (WHO) declared in Geneva that COVID-19 was a Public Health Emergency of International Concern (PHEIC).[1] In order to test the effects of intervention, international researchers have launched a large number of medical research projects. While more and more medical institutions conduct clinical trials, they are also being evaluated simultaneously. Although numerous experts and researchers have analyzed the data, further consideration is necessary.

COVID-19 clinical trial is one of the challenges the world confronts today. The main reason is that in the face of such a global pandemic, researchers have to design and secure clinical trials in a short time. To

address this issue, they need to have access to the most updated information on the research and COVID-19 clinical trials. In general, the results from clinical trials are discrete and expressed in the form of simple data. As these data are difficult to collect statistically, this study utilized computer technology to collect, integrate, transform, and present relevant data and extract valuable information from the China Clinical Trials Registry (ChiCTR) and the ClinicaTrials.gov website. After processing and evaluating the data, the characteristics and issues of COVID-19 clinical trials clinical trials were further discussed. In simple terms, this paper aims to act as a complementary decision-making reference for researchers and enable them to quickly access core information.

Methods

Data acquisition strategy

The WHO named the virus as '2019-nCoV' on January 12, 2020 while the International Virus Classification Committee named the virus as 'SARS-CoV-2' on February 11, 2020. To avoid omissions, '2019-nCoV', 'SARS-CoV-2' and 'COVID-19' were used as search terms for this study. The ClinicalTrials.gov website permits the retrieve of results through downloading them. Thus, all data regarding the COVID-19 clinical trials are downloaded locally in CSV format. To extract relevant trial information from the ChiCTR website, the authors implemented a Python script that utilized the Requests module. The data consisted of registration number, registration time, sample size, study type, study design, blinding, primary indicator, intervention, sponsor, inclusion criteria and randomized method.

As of March 28, 2020, all relevant clinical trial records registered on ChiCTR and ClinicalTrials.gov were retrieved.

Data processing

This study used Pandas and Openpyxl module in Python to input/transfer the data into Excel datasheets and to transform them into discrete structures.[2] The post-processing steps include regular expressions, and a dictionary-based approach for extracting certain fields as information was entered in various formats in published results.[3]

Validation of the data acquired on ClinicalTrials.gov: The reliability of the data was ensured by checking the consistency of the number of clinical trial entries in the downloaded CSV file with the retrieved results.

Validation of the data acquired on ChiCTR: The first 10 data were obtained by the program and reorganized in an Excel file. The authors then manually sorted the 10 data, checking that the contents of each field corresponded to each other. After ensuring the correctness the data, a large amount of relevant data was then obtained from the program and the last ten data are checked. For specific data, the authors captured the program exception value via the try/except statement in Python. If the data was null, the contents of the retrieved field would be displayed as 'null'. After obtaining all data, the study team confirmed the accuracy of the quantity by comparing the number of search bars in the website. Finally,

the accuracy of the data was confirmed based on the registration number, and a detailed check of what had 'null' was performed.

All images were visualized by Apache ECharts and published online in HTML format on GitHub.[4] Further details can be displayed by moving and clicking the mouse.

To prevent bias in the results during data screening and conversion, the two authors of this paper processed the data simultaneously and then compared them. Controversial data was processed through consultation with a scientific researcher in the medical field to ensure the results' accuracy.

Results

Number of COVID-19 clinical trials registered on ChiCTR and ClinicalTrials.gov

In total, 744 COVID-19 clinical trials were registered as of March 28 (534 in ChiCTR and 210 in ClinicalTrials.gov). We excluded 67 clinical trials for the following reasons: 10 trials with large amounts of missing data or misinformation, 57 other trials for diagnosis, epidemiological, prevention, basic science, health service, prognosis, and treatment studies. After a scrupulous check on the title and the text, 677 clinical trials were eventually included in our review (Figure 1).

Figure 1 Flowchart of screening process and search results

Trends in the number of registrations over time

As shown in Figure 2, the pandemic was still in its early stages in January with the lowest number (7 of 677, [1.03%]) of registrations. The number of related registrations grew rapidly in February due to the outbreak of COVID-19 in China. The trend curve fluctuates slightly in March. The stagnant growth in registrations from March 20 to 24 may be due to a significant decline in the number of confirmed cases in China at the time. Considering the global spread of COVID-19 and the prevalence of unlisted drugs and vaccines, registrations will continue to increase over time.

Figure 2. The monthly trend of COVID-19 clinical trial registrations (N=677)

An analysis on the trend of overall registrations (Figure 3) demonstrates that the number of interventional studies was significantly higher than the number of observational studies in the early stages of COVID-19. In March, enrollment in observational studies increased significantly. Although the number of interventional trials decreased slightly in mid-March compared to that in February, the trend went upward since March 24. These results were generally correlated to the stage of development of the epidemic, but it was also important to consider the potential influence of other factors (e.g. time differences, unstable website systems, etc.).

Figure 3. Statistics on single-day clinical trial registrations of COVID-19 (N=677)

The sponsor and period of trials

As shown in Table 1. Of the 677 studies, 522 (77.10%) trials were sponsored by hospitals, 74 (10.93%) by colleges and universities, 30 (4.43%) by companies and 27 (3.99%) by institutes. There were also 15 (2.22%) for individual initiators and 9 (1.33%) for others. COVID-19 is an emerging infectious disease that is highly contagious and destructive. To find effective methods of prevention and treatment as soon as possible, trials period was concentrated in an one-year period. 144 (21.27%) Trials period range from 0 to 2 months, 217 (32.05%) from 3 to 6 months and 173 (25.22%) from 7 to 12 months.97(14.33%) Trials period range from 13 to 24 months and 26（3.84%）over 24 months. In addition, 20 (2.95%) trials did not provide a clear period.

Table 1 Information of the sponsor and the period of trials (N=677)

Category	Information	Number of trials	Percentage of total
Sponsor	Hospital	522	77.10%
	Colleges and universities	74	10.93%
	Company	30	4.43%
	Institute	27	3.99%
	Personal	15	2.22%
	Other	9	1.33%
period	0–2 months	144	21.27%
	3–6 months	217	32.05%
	7–12 months	173	25.55%
	13–24 months	97	14.33%
	>24 months	26	3.84%
	Not provided	20	2.95%

Status of recruitment and approval by the Ethics Committee

In the 677 studies, 332 (49.04%) clinical trials recruited volunteers while 292 (43.13%) did not; 397 (58.64%) clinical trials were approved by ethics committees while 83(12.26%) were not (Table 2). Notably, 24 of 332 (7.23%) trials in recruitment and 3 of 25 (12.00%) completed trials have not been approved by the Ethics Committee. Approval by the Ethics Committee is a prerequisite for clinical trial registration,[5] but the urgency to suppress further exacerbation of the COVID-19 outbreak has resulted in some unregistered trials.

Table 2 Status of recruitment and approval by the Ethics Committee (N=677)

Recruiting status	Approved by the Ethics Committee			Total
	Yes	No	Not provided	
Active, not recruiting	0	0	5	5
Completed	13	3	9	25
Enrolling by invitation	0	0	3	3
Not yet recruiting	150	54	88	292
Recruiting	223	24	85	332
Withdrawn, Suspended or Terminated	11	2	7	20
Total	397	83	197	677

Characteristics of subjects

As shown in Table 3, basic characteristics of subjects were classified according to the 'inclusion criteria' of 677 clinical trials. The main types of subjects included confirmed cases (77.25%), unconfirmed cases (13.00%), suspected cases (6.50%) and rehabilitation patients (2.36%). Since most trials received cases of different grades for COVID-19, the total number of different cases was higher than the total number of confirmed cases. In studies with confirmed cases, severe cases were selected more frequently (441 of 532 [84.32%]) as a condition for inclusion. In studies of unconfirmed cases, there were more (38 of 88 [43.18%]) trials with close contacts as the main subjects. The age demographics of the subjects was also accounted in this study. There were 375(55.39%) trials that included both adults and elders, and 233(34.42%) trials included children, adults and elders at the same time. Fewer (59 of 677, [8.71%]) trials were conducted for a single age group.

Table 3 Characteristics of subjects（N=677）

*All age groups were defined by ClinicalTrials.gov: age ≤ 17 is 'Child'; 18 to 64 is 'Adult' and ≥ 65 is 'Older Adult'.

Category	Information	Number of trials	Percentage of total
Type of subject	Confirmed Cases	523	77.25%
	Mild Cases	316	60.42% (N=523)
	Moderate Cases	390	74.57% (N=523)
	Severe Cases	441	84.32% (N=523)
	Critical Cases	374	71.51% (N=523)
	Unconfirmed cases	88	13.00%
	Close Contact	38	43.18% (N=88)
	Healthy Volunteers	29	32.95% (N=88)
	Patients with other diseases	21	23.86% (N=88)
	Suspected Cases	44	6.50%
	Rehabilitation Patients	16	2.36%
	Not Provided	6	0.89%
Age group	Adult, Older Adult	375	55.39%
	Child, Adult, Older Adult	233	34.42%
	Adult	46	6.79%
	Child, Adult	10	1.48%
	Child	10	1.48%
	Older Adult	3	0.44%

Design of intervention model and blinding in interventional clinical trials

A summary of the statistics for the interventional study types and blinding is shown in Table 4. The main methods of interventional study are randomized parallel assignments (70.27%), the non-randomized parallel assignments (9.58%) and single group assignments (12.29%). Control and experimental groups in randomized parallel trials are observed experimentally simultaneously, which helps eliminate errors caused by factors such as time and experimental conditions. Since there is not any specific drug for treating COVID-19 and its survival period is longer than that of other epidemics, most of interventional studies were designed by a randomized parallel assignment.

Blinding is an important tool for reducing subjects' perceptions of treatment allocation schemes between groups, eliminating bias and improving the scientific and validity of trials.[6] Interventional studies with blinding are listed as the following: double- blind accounted for 11.79%; single-blind for 5.41%, open label for 44.23% and not provided for 38.57%.

Table 4 Design of intervention model and blinding in interventional clinical trials (N=407)

Intervention Model	Blinding				Number of trials [n (%)]
	Open Label [n (%)]	Single [n (%)]	Double [n (%)]	Not provided [n (%)]	
Randomized Parallel	132 (32.43)	20 (4.91)	47 (11.55)	87 (21.38)	286 (70.27)
Non-randomized Parallel	9 (2.21)	0	1(0.25)	29 (7.13)	39 (9.58)
Single Group	30 (7.37)	0	0	20 (4.91)	50 (12.29)
Sequential	7 (1.72)	1 (0.25)	0	10 (2.46)	18 (4.42)
Crossover	1 (0.25)	1 (0.25)	0	1 (0.25)	3 (0.74)
Other	1 (0.25)	0	0	10 (2.46)	11 (2.70)
Total	180 (44.23)	22 (5.41)	48 (11.79)	157 (38.57)	407 (100)

Groups

The number of groups involved in COVID-19 clinical trials were counted (Figure 4). 265 trials involved a single group (39.14%), 323 trials involved two groups (47.71%), 55 trials involved three groups (8.12%), and 34 trials involved at least four groups (5.03%). During COVID-19, most trials were divided into two groups, one being controlled studies. This categorization allows differences across groups to be efficiently assessed, benefiting the discovery of 'potent drugs' that can counter the virus.

Figure 4 Groups for all clinical trial registrations (N=677)

Sample size

Directly related to the reliability, reproducibility and efficiency of clinical trials, , the sample size of a clinical trial is critical and demands deliberate consideration. It was noted that the sample size of clinical trials was mainly within the range of 0-299 (Figure 5). The number of participants in interventional and observational trials peaked in the sample range of 100-299. Studies with more than 300 participants accounted for a smaller portion (189 of 677 [27.92%]). There were 29 (4.28%) and 50 (7.93%) observational studies in the sample interval of 500 to 999 and >1000, respectively. There were more observational studies with >500 participants than interventional studies.

Figure 5. Relationship between different study (interventional and observational study) types and sample size (N=677)

Primary endpoint of interventional clinical trials

When designing a clinical trial, one of the most challenging and critical issues is how to select the primary endpoint used to assess efficacy. Given that a clinical trial should provide reliable evidence for its benefits and risks, the primary endpoint is preferably an outcome measure that clearly informs the patients of the benefits.[7] Among 407 interventional studies, the required time for clinical recovery constituted 13.51%, clinical parameters and laboratory index for 11.55%, the change of pneumonia

severity for 11.06%, questionnaire or scales for 9.83%, virus negative conversion rate of time for 8.11 %, the cure rate for 7.37%, and the mortality rate for 6.14% (Figure 6).

Figure 6. Statistics of primary endpoint (N=407)

Interventions

Interventions from 407 interventional trials were discussed in this section. Table 5 presents the details. Chemical or biological drugs accounted for 43.49%, of which 14.50% were antivirals, 8.85% were antimalarial drugs, and 7.86% were antineoplastics and immunomodulators. Clinical trials involving Traditional Chinese Medicine (TCM) or integrated medicine accounted for 24.08%, and cell therapy, behavioral intervention and medical instruments respectively accounted for 8.60%, 7.13% and 4.91%. In addition, five vaccine clinical trials for COVID-19 are in progress and their registration numbers are NCT04299724, NCT04276896, NCT04283461, NCT04313127 and NCT04324606.

Table 5 Statistics of interventions (N=407)

Category	Number of trials	Percentage of total
Chemical or Biological	177	43.49%
Antivirals	59	14.50%
Antimalarials	36	8.85%
Antineoplastics and Immunomodulators	32	7.86%
Antipyretic Analgesics	19	4.67%
Glucocorticoids	9	2.21%
Mucolytics	7	1.72%
Other	16	3.93%
TCM or Integrated Medicine	98	24.08%
Cell Therapy	35	8.60%
Plasma	15	3.69%
Vaccine	5	1.23%
Medical Instruments	20	4.91%
Behavioral Intervention	29	7.13%
Psychological intervention	4	0.98%
Other	23	5.65%

Combination of antiviral drugs and other drugs

This section further studied the interventional clinical trials of the 59 antiviral drugs aforementioned, and analyzed the combined use of antivirals with other drugs (Figure 7). The most commonly used antivirals were Lopinavir/ritonavir (LPV/r), Arbidol and Ribavirin. The drug with which they were most frequently combined was interferon, followed by Favipiravir with Tocilzumab and Darunavir with Cobicistat.

Figure 7. Relationship between antivirals and other drugs

* The size of the node in the figure corresponds to how many times it is used.

* The thickness of the connection between the drugs indicates the closeness of the joint use between the two.

Discussion

As a major component of clinical evidence, clinical trials play an important part in clinical research.[8] For safety concerns, clinical data should be strictly and efficiently managed during COVID-19. Accurate decisions can only be made if medical records are uniformly submitted in a timely manner and analyzed after reasonable assessment.

The trend curve shows that COVID-19 clinical trials were very prevalent. Up until March 28, 407 interventional studies and 270 observational studies had been registered. The intervention models for the intervention studies were mainly randomized parallel and single group assignments, and most of their blinding designs were open label. Considering the current diversity of subjects, the various design combinations are of great research value for the scientific and efficient completion of clinical trials, regarding both treatment and prevention of the virus.

Researchers should design clinical trial protocols that are both reasonable and efficient based on the actual context. Randomized controlled trial (RCT) is the 'Gold Standard' for evaluating causal effects in clinical research, allowing subjects to be fairly and randomly divided into experimental or control groups independent of their subjective preferences.[9] But it is often time consuming and resource intensive. When confronting an infectious pandemic like COVID-19, researchers need to complete the trial in an effective time period. It can be seen from the statistics that 53.32% of the clinical trials limited the time interval to be less than six months. Large-scale RCT studies can improve the validity of statistical tests while a timely COVID-19 clinical trial can appropriately lessen the number of infected subjects. Depending on the specific data studied, a sample size set between 100 and 299 may be appropriate. In addition, the sample

size of some trials was too small (<20) and it is recommended that the number of subjects may be increased appropriately to ensure the validity of the results of the trial if possible.

The primary endpoint should be targeted based on factors such as the nature of the trial and subject status. For example, since mild patients have a lower mortality rate, researchers can set the clinical recovery time or cure rate as a primary endpoint. One of the reasons for the difficulty of prevention and control for COVID-19 is the high specificity and low sensitivity of the nucleic acid test for the virus, which does not exclude the presence of some false-negative patients.[10] In order to improve the accuracy of the detection, some institutions have conducted clinical studies on virus detection methods. In this case, the detection characteristics of the virus can be selected as the primary endpoint. In general, the establishment of an endpoint indicator needs to be determined on the basis of specific clinical trials, and the bias of the measures needs to be minimized.

The current TCM or integrated medicine trials were relatively prevailing, accounting for 24.08% of the 407 interventional studies. Integrated medicine can both complement and improve clinical efficacy. Currently, some researchers have found that Lianhuaqingwen has antiviral and anti-inflammatory properties against COVID-19,[11] an in-depth study of which may bring some positive effects to the treatment of COVID-19.

In terms of antiviral drug selection, most trials have chosen to combine LPV/r with interferon, a similar design approach that was used in clinical trials for the treatment of Middle East Respiratory Syndrome (MERS).[12] Whereas for critically ill COVID-19 adult hospitalized patients, the study team did not observe a significant therapeutic effect of LPV/r compared to standard treatment cases.[13] Since COVID-19 does not yet have specific drugs for treatment, the present study has visualized the use of antivirals in combination with other drugs to find multiple drug combination options, such as Favipiravir with Tocilzumab and Darunavir with Cobicistat.

Also, antimalarials (such as Chloroquine and Hydroxychloroquine) may be helpful for viral therapy.[14] Trials related to cell therapy and plasma in recovered individuals are also ongoing. Considering the fact that frontier workers also face great psychological pressure under long, highly intense, demanding, and high-risk working conditions, some researchers mainly used health questionnaires to understand their psychological changes and the reasons behind them, in order to establish timely mental counseling programs in case of emergency epidemics. In general, there are more treatment options for COVID-19 than what was available during Severe Acute Respiratory Syndrome (SARS),[15] with a wider range of options and considerations for subjects.

In addition, the registration of clinical trials should be regularized while a large number of clinical trials are conducted rapidly in a short period of time. To protect the safety and legitimate interests of the subjects, clinical trials should be approved by an ethics committee. However, some clinical trials of COVID-19 that have not yet been approved by the ethics committee have begun enrolling subjects. These studies should be supplemented with relevant information and submitted as soon as possible to ensure

that the trial can be conducted. According to the statistics, 157 (38.57%) studies did not provide information on the design of blinding and 20 (2.95%) studies did not provide time intervals. However, this information may be meaningful to some researchers and should be updated as soon as possible.

This study is innovative for using data visualization to mine and analyse the registration characteristics and current progress of COVID-19 clinical trials and to eventually find potential antiviral combinations for investigators through a joint network. However, most of the trials are inconclusive, and we will be following up on them continuously to examine the validity and reliability of their design in depth. A limitation of this study is that it is time-sensitive, with all data as of March 28 and no updates after that.

Conclusion

In this study, trial registration data from ChiCTR and ClinicalTrials.gov website were collected and processed, followed by research and a visualization analysis of 677 COVID-19 clinical trial registration features. This study provides clinical investigators with recent trial design information and new ideas for early validation of efficacy, providing data support to guide the next phase of virus control efforts.

Abbreviations

WHO: World Health Organization

PHEIC: Public Health Emergency of International Concern

ChiCTR: China Clinical Trials Registry

TCM: Clinical trials involving Traditional Chinese Medicine

LPV/r: Lopinavir/ritonavir

RCT: Randomized controlled trial

MERS: Middle East Respiratory Syndrome

SARS: Severe Acute Respiratory Syndrome

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data analyzed in this study are available on the ChiCTR and ClinicalTrials.gov website.

Competing interests

All authors declare no conflicts of interest in this work.

Funding

Not applicable

Authors' contributions

X.Q., Cai collated and visualized the data, and was a major contributor in writing the manuscript. Z.L., Zheng collected and collated the data, and adjusted the format of the paper. J.H.,Huang provided professional guidance.All authors read and approved the final manuscript. Q.M., Su is the correspondent for this study.

Acknowledgments

We would like to thank all the health care workers on the front lines of the fight against the pandemic, and the researchers involved in clinical trials.

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Figures

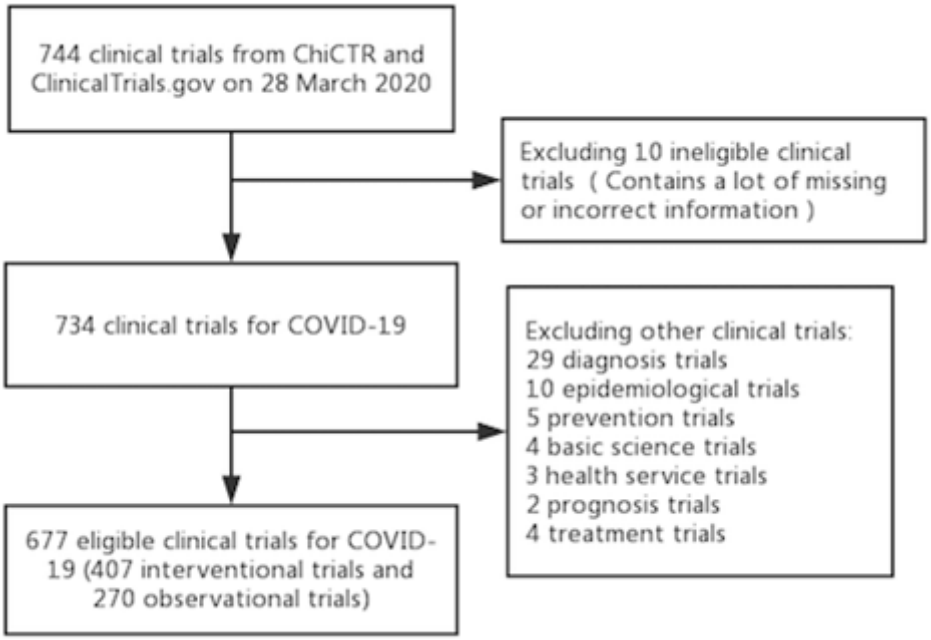

Figure 1

Flowchart of screening process and search results

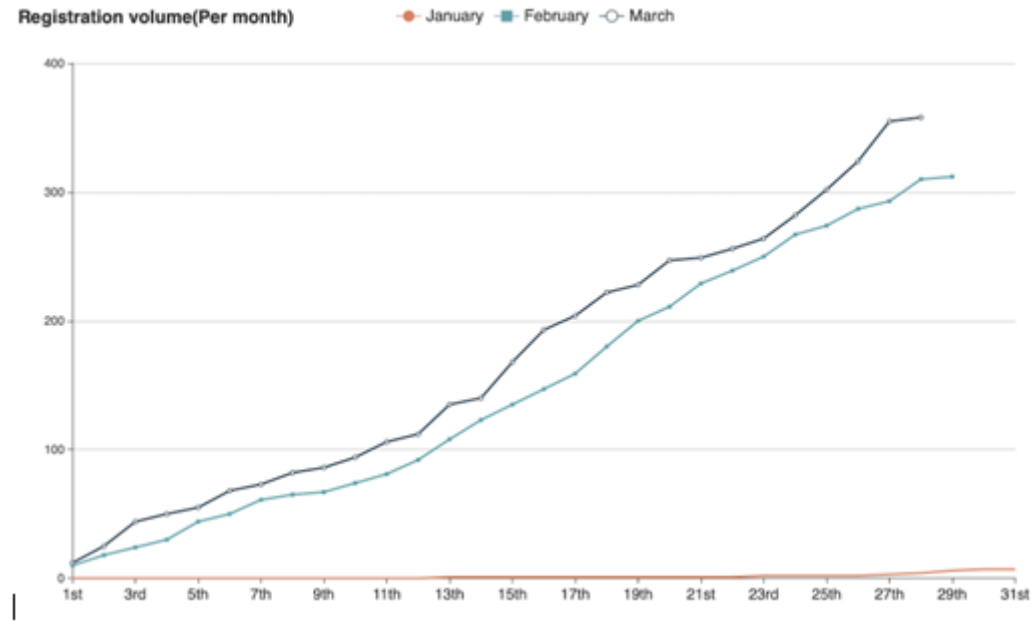

Figure 2

The monthly trend of COVID-19 clinical trial registrations (N=677)

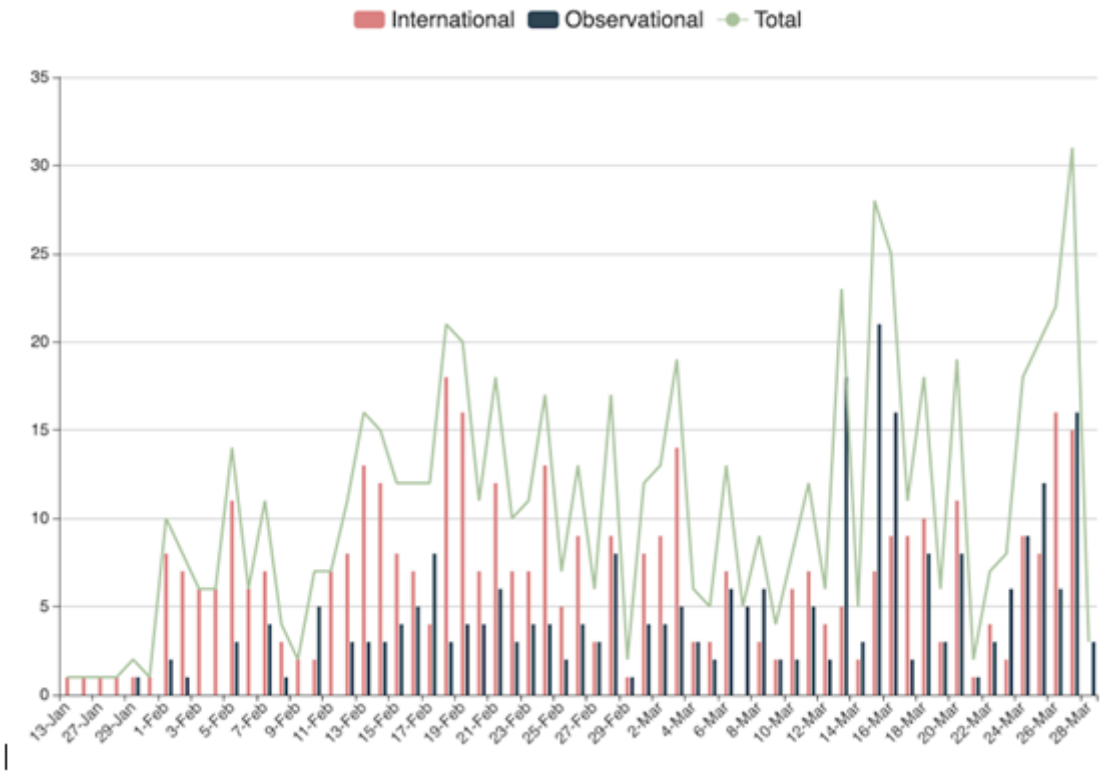

Figure 3

Statistics on single-day clinical trial registrations of COVID-19 (N=677)

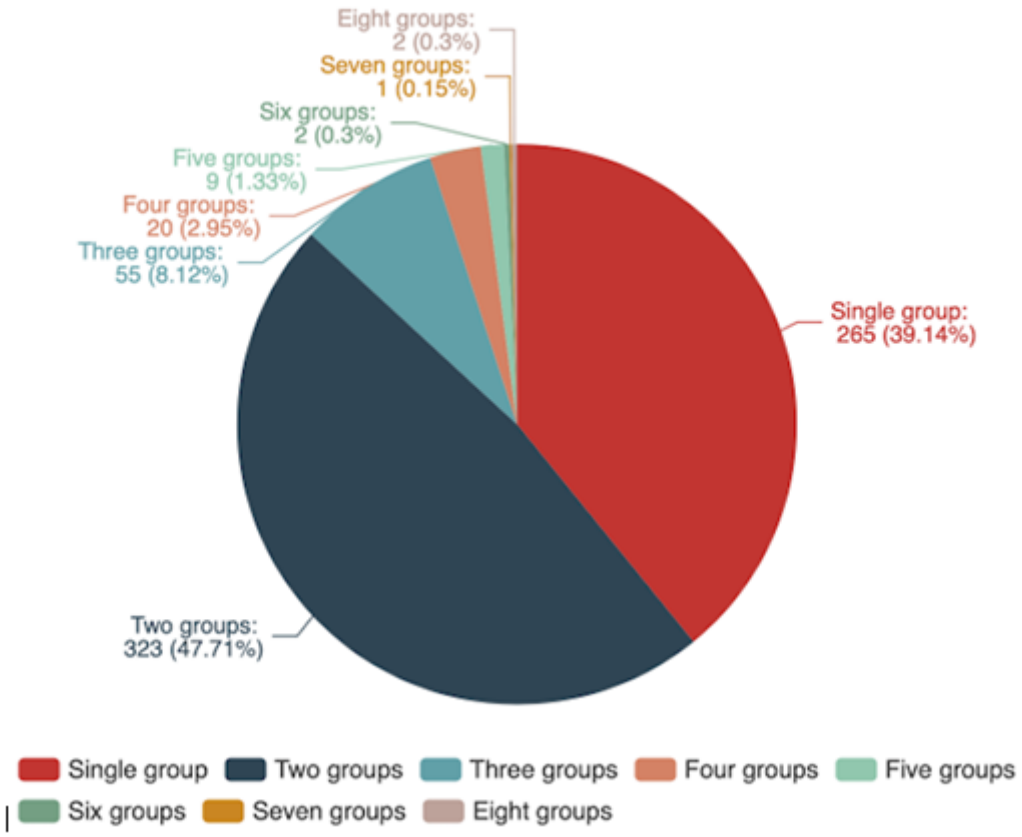

Figure 4

Groups for all clinical trial registrations (N=677)

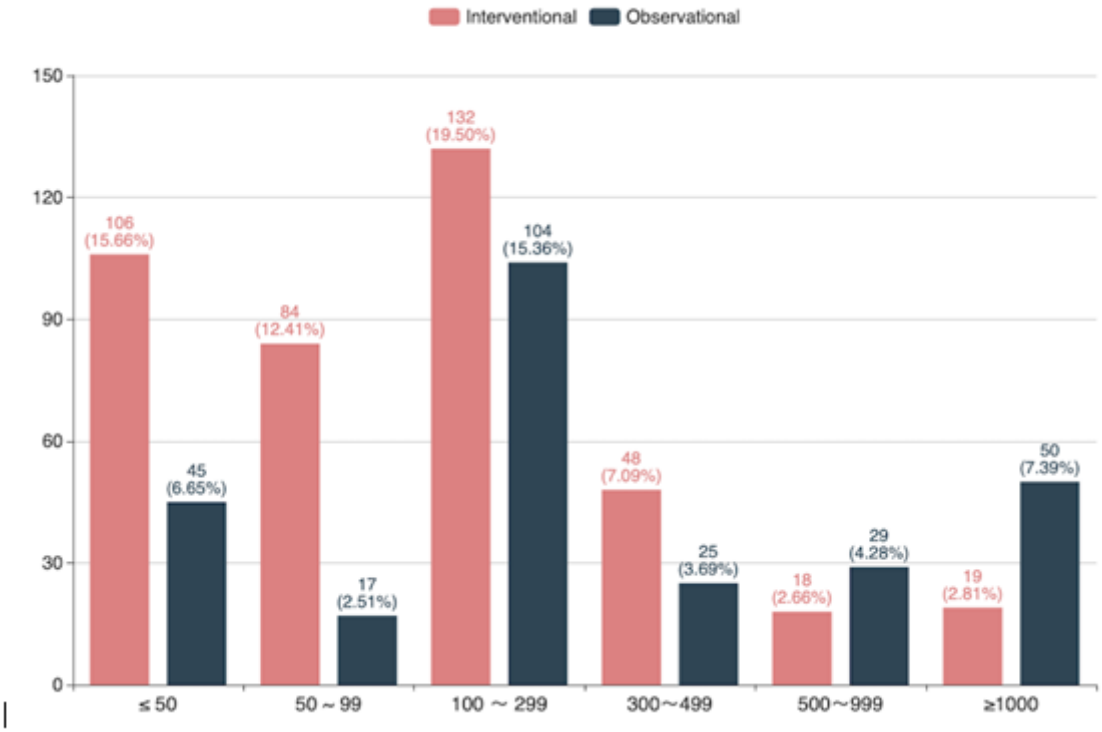

Figure 5

Relationship between different study (interventional and observational study) types and sample size (N=677)

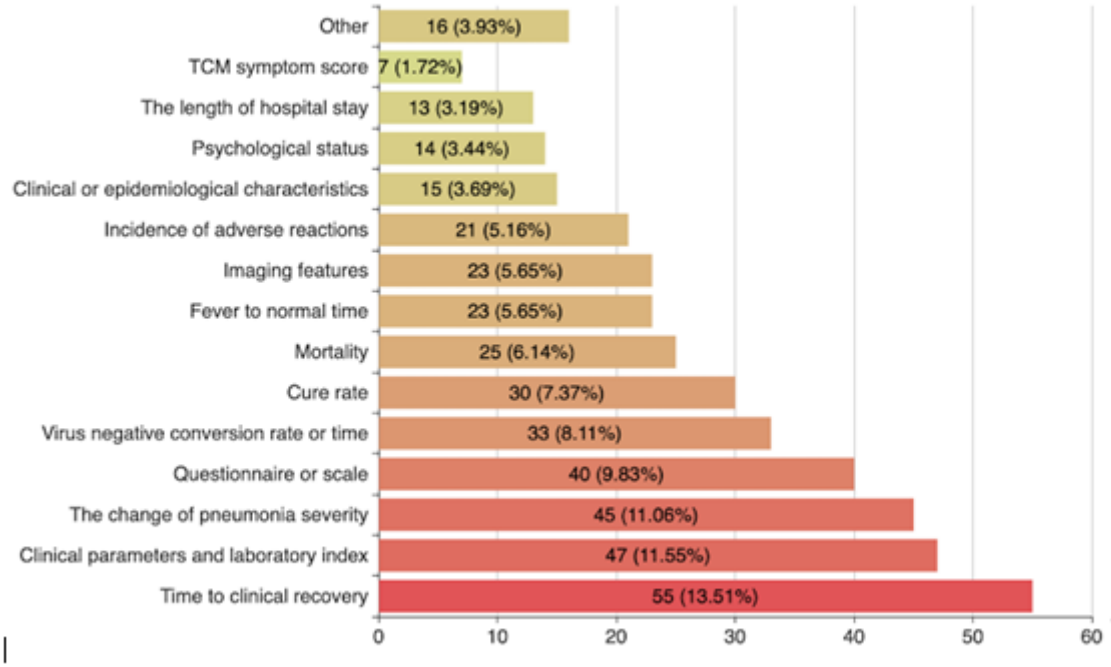

Figure 6

Statistics of primary endpoint (N=407)

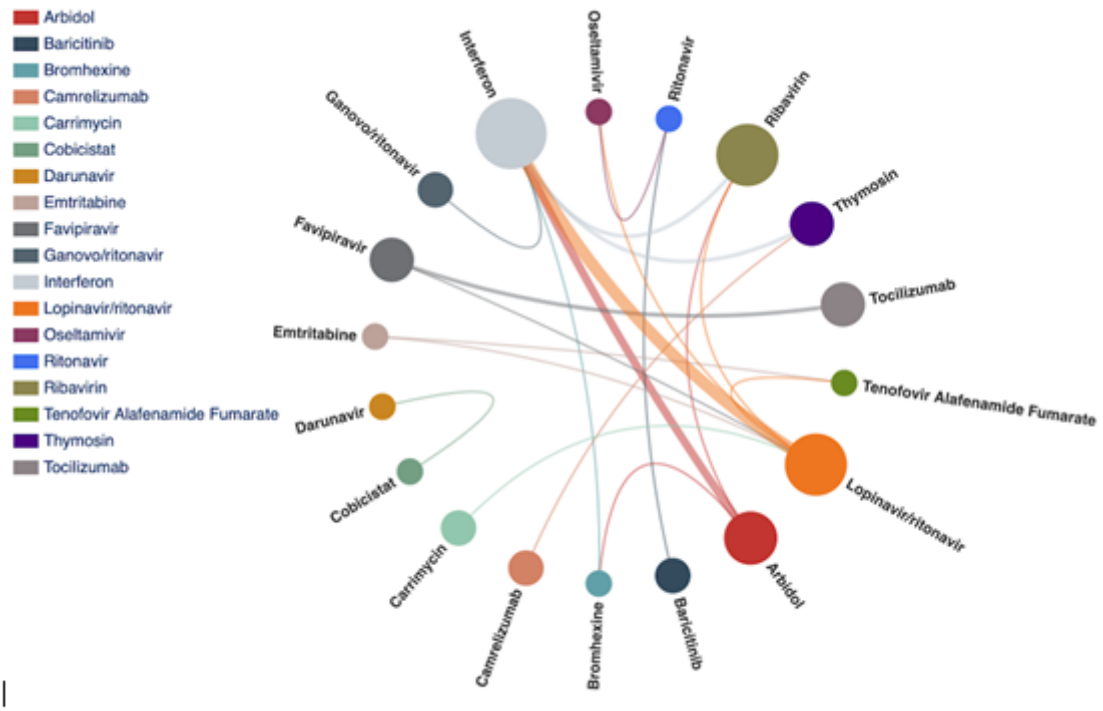

Figure 7

Relationship between antivirals and other drugs * The size of the node in the figure corresponds to how many times it is used. * The thickness of the connection between the drugs indicates the closeness of the joint use between the two.