

Global Trends in Clinical Trials-SARSCOV-2

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Research Article

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Abstract

It was on March 11, 2020, the World Health Organization (WHO) declared the SARS-CoV-2 (COVID-19) outbreak as a pandemic. According to WHO reports, there have been 156,496,592 confirmed cases of COVID-19, including 3,264,143 deaths, globally, as of 8 May 2021. COVID-19 is contributing to an unconscionable loss of life. Several clinical studies involving COVID-19 are currently in human trials. This study is based on a comprehensive analysis of all clinical trials involving COVID-19 as on May 8, 2021. In total, 5619 studies were identified at "ClinicalTrials.gov" and further classified as observational or interventional study types. The results showed a total of 3156 interventional studies and 2429 observational studies. Phase wise distribution of interventional clinical trials indicate that maximum clinical trials are in phase 2 stage. Observational studies has 6 completed studies with results and interventional trial has 23 completed studies with results. Overall, the study reveals the perspective view of the global clinical translational trends involving COVID-19.

Introduction

WHO has defined Coronavirus disease 2019 (COVID-19) as a pneumonia of unknown cause detected in Wuhan, China. It was declared as a Public Health Emergency of International Concern on 30th January 2020 by WHO. Coronaviruses has been described as an enveloped, pleomorphic or spherical particles of 150 to 160 nm in size (Wu et. al., 2020). CoVs contains an envelope of positive single stranded RNA that can be divided into four genera, i.e., alpha, beta, gamma, and delta, of which alpha- and beta-CoVs are known to infect humans (Wilde et.al. 2018). The difference between coronavirus (CoVs) and COVID-19 encodes an additional glycoprotein that has acetyl esterase and hemagglutination (HE) properties as compared with that of coronavirus (Wu et. al., 2020). COVID-19 infects human by binding its S protein to the human cellular receptors angiotensin-converting enzyme 2 (ACE2) (Dong et. al., 2020). Formation of virion-containing vesicles made of glycoproteins and nucleocapsid proteins that fuses with the plasma membrane helps to release the virus into the host cell (Sevajol et. al., 2014). This binding is weaker for SARS-CoV, than that SARS-CoV-2 that causes less severe infection in patients than SARS-CoV (Dong et. al., 2020).

SARS-CoV continues to rapidly spread throughout the world and its transmission and infection incidence varies greatly among different countries. It is unfortunate that the COVID-19 pandemic may lead to constantly increase burdens of morbidity and mortality and simultaneously disrupting societies and economies at the global level (Lazarus et.al. 2021). In the first week of May 2021, Brazil's total death toll from COVID-19 passed 400,000 and in India, the pandemic is taking around 3,500 lives every day (Editorial Nature, 2021). This has prompted a global response to tackle the situation in several ways-scientifically, economically or politically. Several country are involved in multiple diagnostic, therapeutic, and preventive interventions for COVID-19 are being trialed. Emergency efforts are underway to find optimum medical products to fight COVID-19 pandemic. COVID-19 pandemic threatens a global surge in substandard and falsified medical products either directly or indirectly related to COVID-19. The aim of the study was to perform a comprehensive analysis of all clinical trials involving COVID-19 as on May 8, 2021.

Methods

Systematic search of databases

The aim of the study was to perform a comprehensive analysis of all clinical trials involving COVID-19 as on May 8, 2021. First a search was performed in the database "ClinicalTrials.gov" using the search terms "COVID-19" OR "SARSCOV-2". In total 5619 studies were identified at "ClinicalTrials.gov". The studies were generally classified as observational or interventional study types.

Results

Geographical distribution of clinical trials (total number) involving COVID-19 varied at the global level and a total of 5619 studies were found for COVID-19. Of these, 3156 studies were found for interventional and 2429 for observational studies (Fig. 1B & C).

Observational studies has 6 completed studies with results and interventional trial has 23 completed studies with results. Phase wise distribution of interventional clinical trials indicate that maximum clinical trials are in phase 2 stage (Fig. 3A). The duration of the completion of the studies varied with maximum duration for study completion is up to 12 years (Fig. 3B).

Global distribution of clinical trials involving COVID-19:

All clinical trials were classified according to the region or area they were conducted in. Overall,

29% (2077) of all trials were conducted in Europe, North America 22% (1573), United states 18% (1294), Middle East 6% (418), South America 5% (346), Africa 4% (300), East Asia 4% (294), South Asia 2% (165), Canada 3% (210), Mexico 2% (137), North Asia 2% (124), Southeast Asia 1% (108), Pacifica 1% (46), Central America 1% (39), Japan 0% (36) (See Fig. 1A & B). The study could be classified as interventional trial in 56.16% (3156) and as observational in 42.22% (2429) (See Fig. 2A & B). When focusing on the global distribution of the clinical trials region wise for the interventional trial, it was 26% (1120) in North America, United sates 21% (918), Europe 20% (881), South America 6% (257), East Asia 5% (200), Middle East 4% (194), Canada 3% (150), Africa 3% (146), North Asia 2% (91), Mexico 2% (106), Southeast Asia 2% (79), Pacifica 2% (35), Japan 1% (28), Central America 1% (25) (See Fig. 3B). Similarly, for observational studies, the trend in global distribution varied as Europe 43% (1191), North America 16% (434), United sates 13% (357), South America 3% (89), East Asia 3% (92), Middle East 8% (221), Canada 2% (59), Africa 6% (152), North Asia 1% (33), Mexico 1% (31), Southeast Asia 1% (29), Pacifica 0% (8), Central America 1% (14), Japan 0% (6) See Fig. 3C). Overall, these results indicate that, most of the clinical studies are performed in the USA and Europe with the majority of them being interventional. This trend can also be observed for other Asian countries.

Of the total global studies, only few clinical studies have been completed with results.

Phase wise distribution of interventional trials and study duration:

Phase wise overview of the interventional clinical trials is represents 42 trials in early phase, 231 trials in phase 1, 194 trials in phase1/2, 696 in phase 2, 205 trials in phase 2/3, 453 trials in phase 3 and 162 trials in phase 4 (Fig. 4A). Overall, results indicate that very few studies are phase 4 and most of the interventional studies are in phase 2. The time duration for the interventional studies from start to completion indicated that maximum duration for few of the studies 10–12 years for its completion. Figure 4B represents an overview of the interventional clinical trials from start to completion in phase 3 (green bar) and phase 4 (blue bar).

Completed clinical trials

Observational studies has 6 completed studies with results and 23 interventional trial has 23 completed studies with results (See Fig. 4A & B). Of these, interventional clinical trials with results include the drug interventions involving COVID-19 as listed in Table 1.

Table 1
Completed interventional clinical trials with results involving COVID-19.

NCT Number	Interventions	Sponsor/Collaborators	Age (years)	Phases	Enrollment	Locations
NCT04392141	Drug: Standard Treatment Drug: Oral administration of Colchicine plus Herbal Phenolic Monoterpene Fractions	Kermanshah University of Medical Sciences	10 and older	Phase 1 Phase 2	120	Iran
NCT04452435	Drug: C21 Drug: Placebo	Vicore Pharma AB Orphan Reach	18 to 70	Phase 2	206	India
NCT04646109	Drug: Ivermectin	Afyonkarahisar Health Sciences University NeuTec Pharma	18 and older	Phase 3	66	Turkey
NCT04542694	Drug: Favipiravir Drug: Standard of care	Promomed, LLC	18 to 80	Phase 3	200	Russian Federation
NCT04401579	Other: Placebo Drug: Remdesivir Drug: Baricitinib	National Institute of Allergy and Infectious Diseases (NIAID)	18 to 99	Phase 3	1033	United Kingdom
NCT04280705	Other: Placebo Drug: Remdesivir	National Institute of Allergy and Infectious Diseases (NIAID)	18 to 99	Phase 3	1062	United Kingdom
NCT04410159	Drug: Povidone-iodine Drug: Essential oils Other: Tap water	Universiti Sains Islam Malaysia Universiti Kebangsaan Malaysia Medical Centre	18 and older	Phase 2	20	Malaysia
NCT04292899	Drug: Remdesivir Drug: Standard of Care	Gilead Sciences	12 and older	Phase 3	4891	United Kingdom
NCT04292730	Drug: Remdesivir Drug: Standard of Care	Gilead Sciences	12 and older	Phase 3	1113	United Kingdom
NCT04358081	Drug: HCQ Drug: HCQ + AZT Drug: Placebo	Novartis Pharmaceuticals Novartis	18 and older	Phase 3	20	United States
NCT04523831	Drug: Ivermectin and Doxycycline Drug: Standard of care	Dhaka Medical College	18 and older	Phase 3	400	Bangladesh
NCT04422561	Drug: Ivermectin Tablets	Zagazig University	16 to 70	Phase 2 Phase 3	340	Egypt
NCT04343092	Drug: Ivermectin (IVM)	University of Baghdad	18 and older	Phase 1	16	Iraq
NCT04491240	Drug: EXO 1 inhalation Drug: EXO 2 inhalation Drug: Placebo inhalation	State-Financed Health Facility "Samara Regional Medical Center Dynasty" Clinics of the Federal State Budgetary Educational Institution SSMU Samara Regional Clinical Hospital V.D. Seredavin	18 to 65	Phase 1 Phase 2	30	Russian Federation
NCT04491994	Drug: HCQ	UNICEF Pak Emirates Military Hospital Rawalpindi, Pakistan	18 to 80	Phase 3	540	Pakistan

NCT Number	Interventions	Sponsor/Collaborators	Age (years)	Phases	Enrollment	Locations
NCT04390022	Drug: Ivermectin Drug: Placebo	Clinica Universidad de Navarra, Universidad de Navarra Barcelona Institute for Global Health	18 to 59	Phase 2	24	Spain
NCT04365153	Drug: Canakinumab Injection 600mg Drug: Canakinumab Injection 300mg Drug: Placebos	The Cleveland Clinic Novartis	18 and older	Phase 2	45	United States
NCT04343261	Biological: Convalescent Plasma	Saint Francis Care	18 to 90	Phase 2	48	United States
NCT04332991	Drug: Hydroxychloroquine Drug: Placebo	Massachusetts General Hospital National Heart, Lung, and Blood Institute (NHLBI)	18 and older	Phase 3	479	United States
NCT04402970	Drug: Dornase Alfa Inhalation Solution	University of Missouri-Columbia	18 and older	Phase 3	30	United States
NCT04490239	Drug: Intranasal heparin sodium (porcine)	Joshua Sharp University of Mississippi, Oxford	18 to 65	Early Phase 1	6	United States
NCT04406194	Drug: FAVICOVIR 200 mg Film Tablet Drug: AVIGAN 200 mg Film Tablets	Atabay Kimya Sanayi Ticaret A.S. Novagenix Bioanalytical Drug R&D Center Farmagen Ar-Ge Biyot. Ltd. Sti	20 to 40	Phase 1	30	Turkey
NCT04400682	Drug: FAVIRA 200 MG Film Tablet Drug: AVIGAN 200 MG Film Tablets	Novelfarma İlaç San. ve Tic. Ltd. Sti. Novagenix Bioanalytical Drug R&D Center Farmagen Ar-Ge Biyot. Ltd. Sti	20 to 40	Phase 1	30	Turkey

Discussion

“There is almost nothing surprising about COVID-19 pandemic” if we remind ourselves from the SARS outbreak that occurred in late 2002 and 2003, not long after China had resumed sovereignty over Hong Kong in 1997. Several countries are involved in multiple diagnostic, therapeutic, and preventive interventions for COVID-19. Lack of any specific therapeutic agents due to COVID-19 pandemic and substantial mortality has led to various challenges to find new treatments. The lack immunity to SARS-CoV-2 makes human population susceptible to the novel virus. COVID-19 impact is on the global level. Making decisions to mitigate COVID-19 with limited knowledge may affect directly the level of the public health response or clinical management. Patients should not be given drugs of unknown efficacy, however, for patients with life-threatening infections, off-label or compassionate use of drugs should be considered ethical (Zhang and Qian, 2020).

Several studies have been focusing on the trends in clinical trials involving “COVID-19” to fight the pandemic. Lythgoe and Middleton published an analysis involving the clinical trials for the management of the COVID-19 Pandemic last year, June 2020. The present study gives a complete overview on clinical trials involving “COVID-19”. One of the major limitation of the present analysis, based on the analysis of clinical trial databases in general, might be a reporting bias. The reason is that all studies may not have been registered on public databases, hence, limiting the representativeness of the data on this type of trials.

Although a large series of clinical trials involving COVID-19 has been registered in public databases, only a small part has been completed with results with only few studies in phase 3 and phase leaving a scope for the focus on the actual implementation of the interventions to eradicate the critical pandemic period being faced at the global scale. A substantial difference has been observed between geographical regions, where the studies have been performed. The greatest part of all trials was performed in

the USA and in Europe and fewer in Asian countries. The major reasons for this may be seen in the differences in legal and/or regulatory restriction etc. The clinical trials have three phases with an increasing number of candidates. But, for COVID-19, scientists are proposing human trials to compress the timeline for developing the vaccine (Lurie et. al., 2020). However, human trials are also a challenge because even after a vaccine has crossed the final clinical trial phase, licencing and quality control takes a lot of time before the vaccine can be launched in the market and made available to the general public (Newton, 2020).

Ivermectin is FDA-approved broad-spectrum antiparasitic agent and now widely been used for SARSVOV-2 infected individuals. However, its antiviral activity against SARS-CoV-2 is currently under investigation in patients, insufficient emphasis has been placed on formulation challenges (Formiga et. al., 20121). Use of ivermectin as prophylactic against SARS-CoV-2 inhibits SARS-CoV-2 replication and likely leads to lower infection rates. Studies suggests the use of Ivermectin as potential off-label prophylactic drug in certain cases to help bridge the time until a safe and effective vaccine for SARS-CoV-2 becomes available (Hellwig and Maia, 2021). Other studies suggest that a five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness (Ahmed et. al., 2021). Use of Favipiravir as pharmacological post exposure prophylaxis for Ebola virus disease prior to COVID-19 outbreak is reported (Jacobs et. al., 2015).

Favipiravir is currently being used as an antiviral for COVID-19. Other studies have indicated a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with lopinavir/ritonavir (Cai et. al., 2020). Favipiravir triphosphate acts as a competitive inhibitor of RNA-dependent RNA polymerase and has activity against influenza A and B (Furuta et. al., 2013; Wang et. al., 2020; Shiraki et. al., 2020). Use of favipiravir in the treatment protocol against SARS-CoV-2 infection is included for many countries including India. It has been shown to have promising results in clinical studies conducted in China, Russia, and Japan, and also more trials are underway in multiple countries, including USA, UK, and India (Joshi et. al., 2021). Remdesivir (RDV) is an inhibitor of RNA-dependent RNA polymerases (RdRps) a novel antiviral drug originally used for the treatment of Ebola virus disease and Marburg virus infections (Chih-Chia Lu et. al., 2020). Remdesivir has a broad-spectrum activity against many virus families e.g. Filoviridae, Paramyxoviridae, Pneumoviridae, and Orthocoronavirinae (such as pathogenic SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) (Sheahan et. al., 2017; Martinez, 2020). It was in USA where the first patient was treated successfully with remdesivir for the progression of pneumonia (Holshue et. al., 2020). Although remdesivir has entered into phase III trial for COVID-19, information regarding the pharmacokinetics of remdesivir in humans is not available (Jean et. al., 2020).

Finding effective therapies across the spectrum of clinical disease states due to variations in clinically different populations also affects the outcomes of the clinical trials processes (Jay et. al., 2020). Racial disproportionality in COVID clinical trials is due to lack of diversity in clinical trials due to long standing medical distrust on the part of minority communities is reported (Chastain et. al., 2020). Covid-19 is thus complicated and referral of patients to clinical trials is critical (David et. al., 2020). Moreover, racial disproportionality in Covid Clinical Trials is also a matter of concern as the data supporting the drug's efficacy and safety in minority groups are limited (Chastain et. al., 2020). For example, the modest benefit to clinical improvement with remdesivir may not be generalizable to minority populations that affect the disease severity and outcomes (Chastain et. al., 2020). Covid-19 is thus complicated and since no proven therapies for Covid-19 exists till today and referral of patients to clinical trials is critical (David et. al., 2020). The case of Covid-19 is an iterative learning process and warrants the critical gaps to be filled. The policy makers must address the underrepresentation of minority groups in clinical trials for COVID-19 (Chastain et. al., 2020).

Conclusion

The lack of immunity to SARS-CoV-2 makes human population susceptible to the novel virus. COVID-19 impact is on the global level. With an increasing number of COVID-19 cases, there has also been an increase in clinical trial registrations. However, a super-fast track of the clinical development of a safe and effective drug interventions for the novel coronavirus at the global scale is utmost today. For both the treatment and prevention from the pandemic, clinical trials need to produce high-quality data to objectively assess potentials therapies for COVID-19 infections.

Declarations

Funding

No funding source.

Conflicts of interest/Competing interests

None

Ethics approval

Ethical approval for this type of study is not required by our institute as there is no animal/human studies included in this manuscript.

Consent to participate

Not applicable

Consent for publication

Consent from all the authors is taken.

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

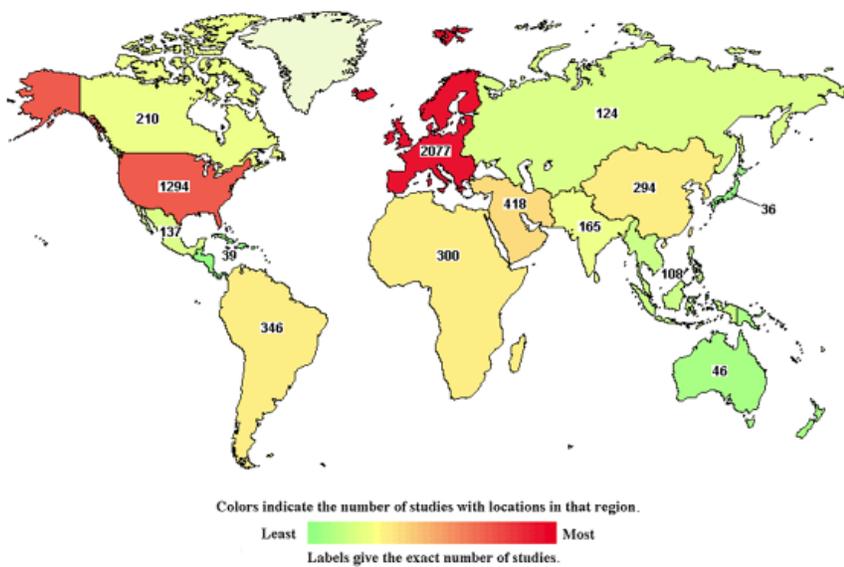
Suman Ray has conceptualized the study, wrote the manuscript and generated the figures. Prashant Dubey provided all kind of support needed to complete the study.

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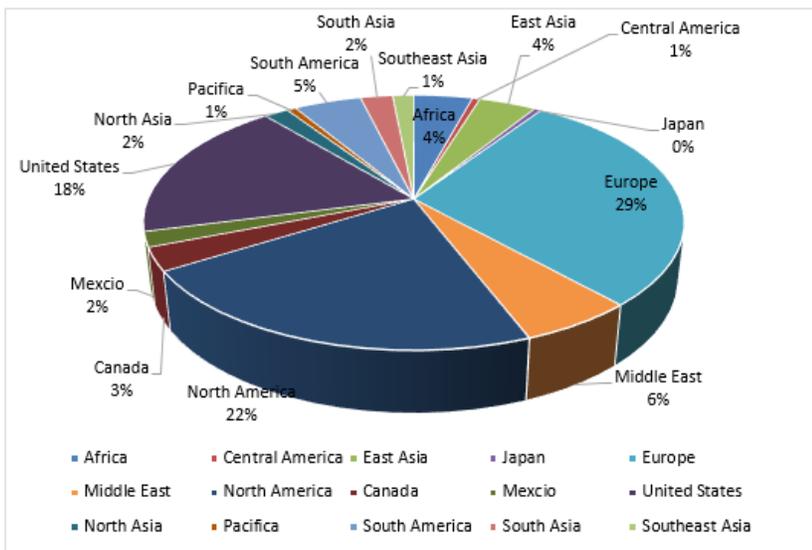
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Figures



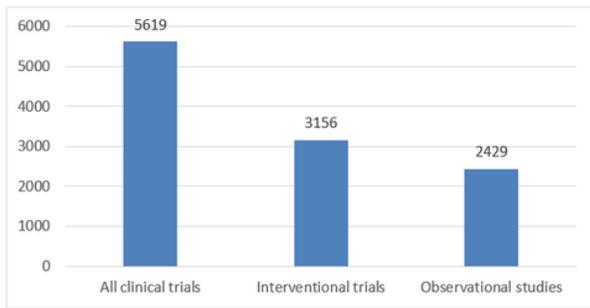
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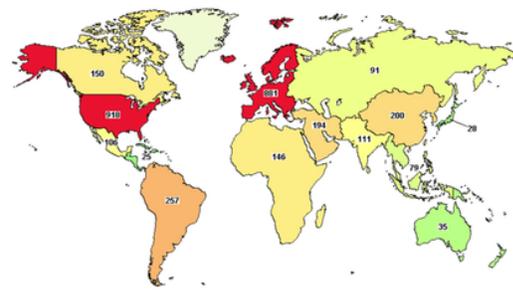
(B)

Figure 1

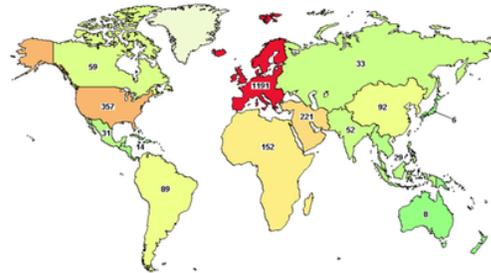
Geographical distribution of clinical trials (total number) involving COVID-19 at the global level-I region wise (A) percentage wise (B). Total 5619 studies found for COVID-19 (date of search 8th May, 2019; ClinicalTrial.gov Database). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.



A



Interventional Studies



Observational Studies

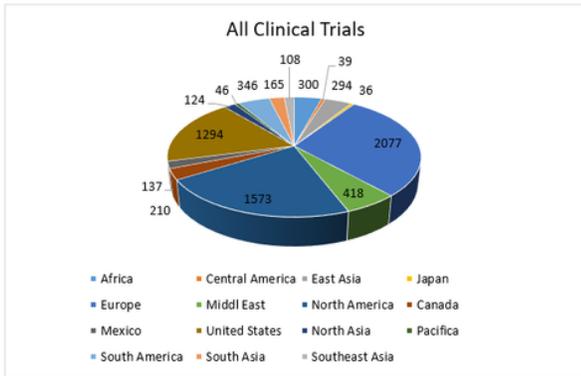
Colors indicate the number of studies with locations in that region.

Least Most
Labels give the exact number of studies.

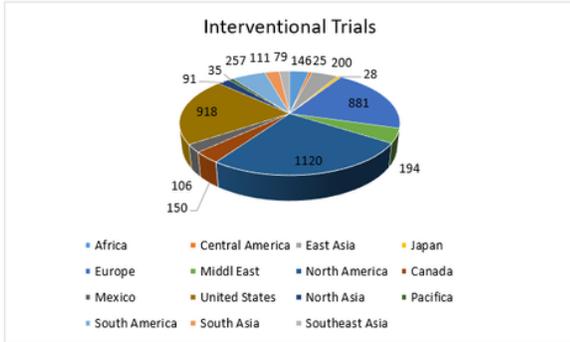
B

Figure 2

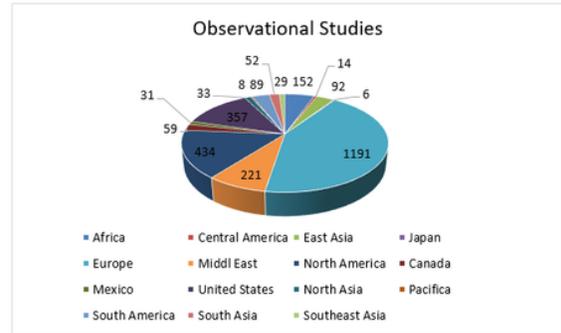
(A). Clinical trials (total number) involving COVID-19 at the global level. All clinical trials=5619, Interventional studies=3156 and Observational studies=2429. (B). Geographical distribution of Clinical trials involving COVID-19: 3156 Studies found for Interventional Studies and 2429 Studies found for Observational Studies. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.



(A)



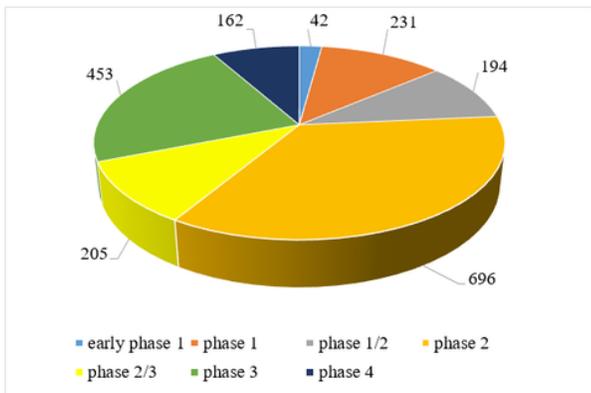
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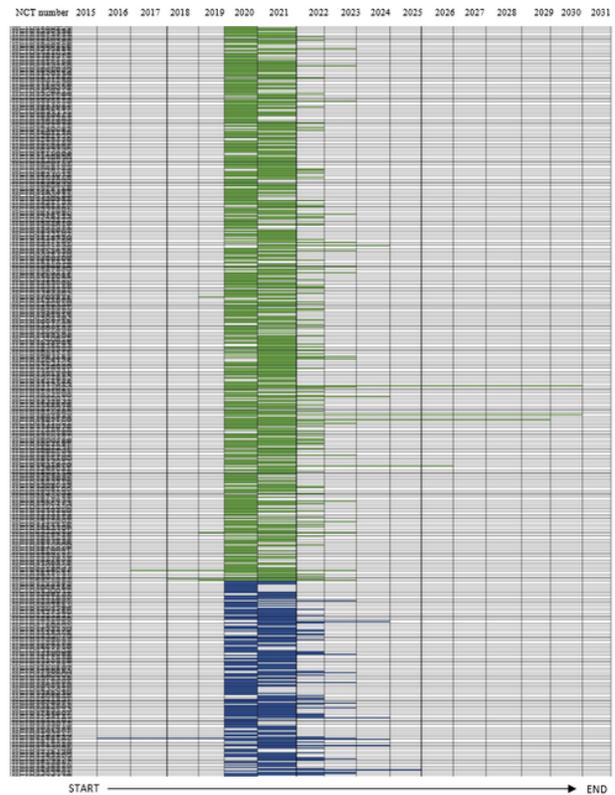
(C)

Figure 3

Global distribution of clinical trials involving COVID-19. (A) All clinical trials (B) Interventional clinical trials and (C) Observational studies.



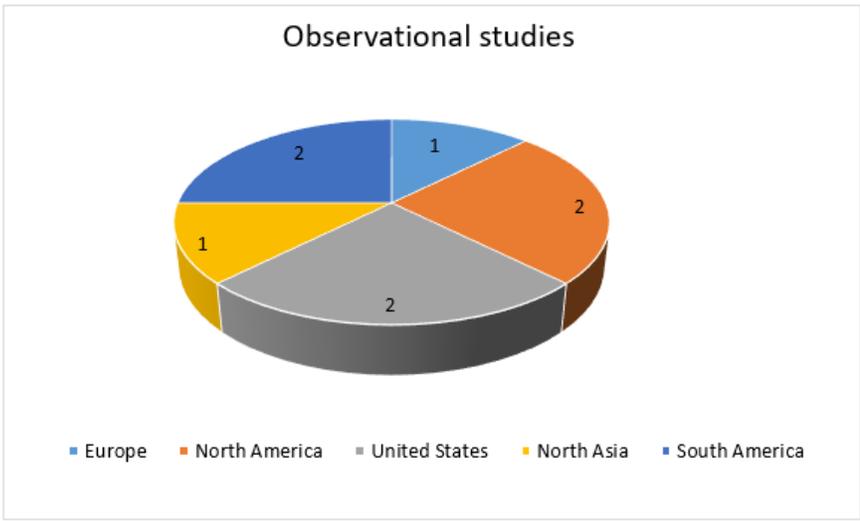
(A)



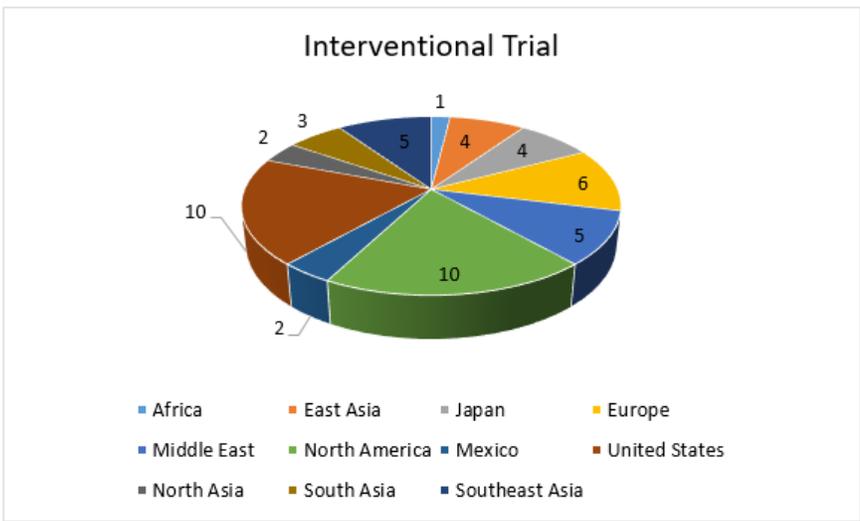
(B)

Figure 4

Overview of the interventional clinical trials (A) Phase wise distribution of interventional clinical trials (B) distribution of interventional clinical trials from start to completion in phase 3 (green bar) and phase 4 (blue bar) studies.



(A)



(B)

Figure 5

Global status of completed clinical trials with results: (A) Observational studies has 6 completed studies with results (B) Interventional trial has 23 completed studies with results.