A Systematic Review of the Clinical Studies in Humans for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2: Clinical Manifestation, Diagnosis and Clinical Trials

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Authors' contributions

This work was carried out in collaboration among all authors. Author GTB is the first and corresponding author designed the review and wrote the first draft of the manuscript. Authors PH, FMN and BAT managed the literature searches and critically revised the intellectual content. All authors read and approved the final manuscript.

Systematic Review

ABSTRACT

Background: In December 2019 Chinese higher officials have acknowledged a number of cases of pneumonia happened in Wuhan, China with those patients who used the seafood from market selling live animals. At the end of December 2019, a kind of new pneumonia feast quickly in Wuhan, China, a novel coronavirus (2019-nCov).
Objective: Systematic analysis of the completed clinical trials in humans due to coronavirus disease in 2019 between January 12, 2020, to May 30, 2020 in 11 countries and possibly to

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recommend the ways to overcome the COV-2 pandemic.

Methods: Clinical studies completed in humans for the treatment of coronavirus disease in 2019 were looked for two databases, namely PubMed and Scopus. Based on the search terms, a total of 369 articles were downloaded. Of the total 369 articles, 38 duplicate articles were removed and 331 articles were screened with objective criterion. From the 331 articles, 168 articles were screened for excluded based on abstract screening and left with 163. Based on the exclusion criteria, 82 review articles, 51 articles not related to SARSCOV- 2 and 4 articles not written in English, in total 137 articles were excluded. Eventually, 26 articles were reviewed with required parameters for conclusive remarks.

Results: Of all the completed human clinical trials conducted in 11 countries obtained from https://clinicaltrials.gov/, the total patients included in the clinical trials from January 12, 2020 to May 30, 2020 were 6130. Out of them 1060 (17.29%) were only females and the rest 5070 (82.71%) were both males and females. From all patients studied, 163 patients were 30-70 years old, 60 patients were 60 years old, 2531 patients were of all age groups and the rest 3376 patients were ≥ 18 years old. Of all the completed clinical trials in 11 countries, eight different interventional models and four study types were used.

Conclusion: From the analysis of segregated results it is apparent that there was inclusion of patients with varied age group in the studies conducted with very less amount of patients from ≤ 18 years old, old age group and only females. The prime reason for least percentage inclusion of different age groups could be the weaker inherent immune response for the pandemic. COVID-19 can cause a conceivably deadly infection in humans. The most typical clinical manifestations reported by patients with coronavirus disease in 2019 were fever, cough, and expectoration. Approval of vaccines for control of COVID-19 is yet to be officially done, although now few vaccines are administered. Knowing the way to enter the cell and the mechanism on how to escape the immune system can be the potential targets to develop a novel SARS-COV-2 treatment protocol.

1. INTRODUCTION

In December 2019, Chinese higher officials have acknowledged many cases of pneumonia happened in Wuhan, China with those patients who used the seafood market selling live animals [1]. At the end of December 2019, a kind of new pneumonia feast quickly in Wuhan, China, a novel coronavirus (2019-nCov) and it has been understood that the responsible cause of pneumonia in a huge number of patients in China. SARS-COV-2 is another name of the novel coronavirus 2019. Last two decades, people have encountered three deadly coronavirus infections. It's the flare-up of Severe Acute Respiratory Syndrome (SARS) in 2002, Middle East Respiratory Syndrome (MERS) in 2012 and COVID-19 in 2019 [2], as a recently developing irresistible infection. Fever, dry cough, shortness of breath and tiredness are the usual signs and symptoms of the new virus. In chronic cases, pneumonia, acute respiratory distress syndrome (ARDS) and death can be happened [3,4]. These are some of the reasons for the virus taking greater attention globally. Following these on the last date of January 2020 World Health Organization (WHO) declared that the outbreak

of coronavirus Disease (COVID-19) in China as a public health emergency and have to be considered internationally [5]. Exigent worldwide reaction to the pandemic disease, novel coronavirus has confronted the teamwork among researchers and scientists that lead to many self-governing activities and trial interventions.

As the current clinical trials listed each week, if impossible day by day, a regular restructured and new information is mandatory to assist the various diagnostic assays and advanced technical approaches are being explored to create awareness about the trials which are properly planned and strengthened to take over the virus and timely answer to most important research questions posed [6].

The developing countries will do the research that retort their settings and the need for repetition of activities has to be decreased. However, during the specified study period of the review there were no officially approved, declared and accessible vaccines or drugs against COVID-19. The techniques for stating about the currently conducting clinical trials in addition to obtaining the relevant data for each

clinical trial is very helpful within the up-to-date research platform [7]. Hence, the purpose of this systematic review is to summarize the analysis with current literature concerning about the completed clinical studies in humans to combat COVID-19 to bring awareness about the COVID-19 pandemic for the public.

2. METHODS

2.1 Search Strategy

Clinical studies completed in human trials for coronavirus disease 2019 treatment were looked in two databases namely, PubMed and Scopus. Based on the search terms, articles available were downloaded. These articles were thoroughly checked and screened for further exclusion in the eligibility criterion.

2.2 Eligibility Criterion

Articles which focus on completed human clinical studies in coronavirus disease 2019 were considered. Review articles, articles not related to SARS-COV-2 and articles not written in English were excluded and forwarded with reviewing the rest of the articles.

2.3 To Avoid Bias

Two investigators (GTB and HP) independently conducted the search, reviewed all the relevant articles and identified the eligible studies. Any discrepancy was resolved by group discussion.

2.4 Data Extraction and Analysis

This systematic review includes study selection, study design, country of the study, study participants and sample size. Each study was analyzed to summarize the already completed human clinical studies in corona virus disease 2019 with concerned study parameters.

3. CLINICAL MANIFESTATION AND VIROLOGICAL EVALUATION

SARS-COV-2 is fundamentally a disease of the upper and lower respiratory tract. The productive multiplication of the infection inside the nasopharyngeal pit is viewed as one reason for the high infectiousness of the virus [8]. Incidentally, the clinical manifestations of COVID-19 will take after those of other viral maladies which influence the lungs; fever, hack and

weakness. As indicated by information from the People's Republic of China, over 80% of infected patients have no signs and symptoms or present just mild manifestations, about 15% exhibited further serious known signs and symptoms including pneumonia and around 5% of patients become sick developing sepsis, septic stun or multi-organ disappointment and the lethality was 1-2% [9,10]. Basically, men were infected more regularly than ladies [11]. The result may change, contingent upon the strength and time of testing. This has all the earmarks of being the situation in Italy. Primarily, sick patients present with the exemplary highlights of ARDS including hyaline membrane development, combined regions in the lungs and atelectasis [12].

Images of the chest obtained from tomography analysis revealed that greater than 50% of the cases were developed ground-glass opaqueness and two-sided shadows [11]; two-sided shadowing was likewise found more than 50% of the cases with conformist X-ray imaging [13]. On admission to the medical clinic, over 80% of patients had developed lymphocytopenia; this was according to the result of laboratory test in a cohort of 173 individuals infected with COVID-19 in Wuhan with the increased percentage of severe disease. Generally, more aged men with comorbidities are bound to become sick and bound to kick the bucket. Around half of the patients with coronavirus disease 2019 have incessant comorbidities. Most of the patients have cardiovascular or cerebrovascular comorbidities or *Diabetes mellitus* [14]. Some patients with an extreme course of sickness had a co-infection with microbes such as fungi and bacteria. Evaluation of culture done in bacteria and fungi had confirmed that *Acinetobacter baumannii, Klebsiella pneumonia, Aspergillus flavus, Candida glabrata* and *Candida albicans* additional to several others [15, 16].

Virological evaluation of COVID-19 recognizes proof for dynamic viral multiplication in the throat. SARS-COV-2 is serious respiratory-tract disease brought about by a coronavirus linked with that caused serious and intense respiratory disorder. These viruses utilize the receptor which is mainly expressed in the lung. Based on this viewpoint, it is thought that SARS has restricted contagious ability. In Germany, the production of viral RNA was examined and the active virus was isolated from patients infected with coronavirus disease 2019. Contagious virus was segregated from throat and lung got tests yet not from stool, blood or urine specimen. Elimination of virus not

expected immediately after seroconversion. The information proposes the multiplication of the virus in the throat and also in the lung is dynamic, subsequently giving information to develop novel infection control protocol [17,18].

4. DIAGNOSIS

In cases dubious for infection with COVID-19, the Robert Koch Institute (RKI) suggests getting parallel specimen from the upper and lower respiratory tract, contingent upon the clinical circumstances. It is imperative to utilize swabs reasonable for identifying the virus (swabs which have the virus with a suitable vehicle medium or if important, dry swabs soaked with a limited quantity of NaCl solution; not agar swabs). The samples ought to be analyzed with RT-PCR to check for viral RNA [19]. COVID-19 patients ought to be ordinarily required to isolate themselves at home for two weeks.

As clinical staffs are an exceptionally constrained asset, taking into account of lack of pertinent staff, the RKI suggested a shorter seclusion period of one week for this gathering. However, the latest information on 11th September 2020 by World Health Organization (WHO) has considered mainly for specimen collection, nucleic acid amplification testing (NAAT), antigen (Ag), antibody (Ab) detection and assurance of quality [20]. In contrast to this, due to the global shortage of materials for the performing test, a CDC 2019 Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)–PCR Diagnostic Panel has been introduced [21]. This tool detects the SARS-CoV-2 virus in the upper and lower respiratory specimens and designed to use with existing RT-PCR testing instrument. This decision was based upon the Emergency Use authorization (EUA) by U.S. Food and Drug Administration (FDA) on 4th February, 2020.

4.1 Laboratory Findings

Various unusual findings like lymphopenia [22], protracted prothrombin time and raised lactate dehydrogenase enzyme were observed in those individuals infected with SARS-COV-2 [23]. Intensive care unit - conceded patients had more abnormal findings compared with non-intensive care unit patients [24]. A few patients had raised levels of serum aspartate aminotransferase, creatine kinase, creatinine and C-reactive protein [23]. Most patients have demonstrated normal range of serum procalcitonin levels [26]. Patients with coronavirus disease 2019 had a significant level of interleukin -7 (IL-7), interleukin -10 (IL-10), interferon gamma (IFN-γ), Interferon-γ-inducible-Protein-10 (IP10) and Monocyte chemotactic protein-1 (MCP1) [24]. All in all, from the studies gathered, ICU-conceded patients had a higher concentration of granulocyte-colony-stimulating factor (GCSF), IP10, MCP1A, Macrophage inflamatoryprotien-1A (MIP1A) and Tumor necrosis factor-alpha (TNF- α) in their serum [22]. A very common reporting was from the findings of the laboratory with increased percentage of lymphopenia in hospitalized patients affected with COVID-19. Eventually this condition indicates low level of white blood cells weakening the immunity of affected individual leading to early death.

4.2 Radiology Findings

Based on the findings of disease development, early diagnosis, age, comorbidity and status of the immunity from the result of radiology examination differed from patient to patient [27]. The result of chest computed topography (CT-Scan) of 41 COVID-19 patients revealed that all had developed pneumonia with unusual findings [24]. The outcome of additional six SARS-COV-2 cases also exhibited significant multi-focal patching ground glass opacities adjacent to the peripheral segments of the lungs [25]. Data from the researches demonstrated that the distinctive of chest CT-scan findings are two-sided pulmonic parenchymal ground-glass and consolidative respiratory opacities [28]. The consolidated lung lesions among patients at least five days from illness beginning and those greater or equal to 50 years of age contrasted with less than or equal to 4 days and those greater or equal to 50 years of age, correspondingly [29]. As the infection course proceeds, mild to moderate development of disease were noted sometimes which showed by extension and expanding thickness of lung opacities [30]. Bilateral multi-lobular and subsegmental zones of consolidation are the main results on chest CT-scan of ICU-conceded patients [24]. The results of 99 patient radiology investigation showed one patient had already developed pneumothorax [22]. However, the findings from radiology are used controversially as an additional or substitution diagnostic test by some and various related organizations state that CT test should not be believed as a diagnostic or screening tool for COVID-19. Tables 1 to 5 summarize the details on the completed clinical trials with study parameters, sponsors of clinical trials, models

used in the study and outcomes of the clinical trials [31].

5. CLINICAL TRIALS ON POTENTIAL ANTIVIRAL DRUGS

Even though there is no confirmed drug to cure patients infected with coronavirus disease 2019, there are numerous clinical trials popping anti-viral drugs. Based on the target, the treatments were grouped into two parts. The first one is to kill the virus or inhibit its entrance in to the host cells. The second one aims to strengthen the protection capability of the immune system. Majority of the antiviral drugs currently involved in the clinical trial were intended for the treatment of other pathogenic microbes. Now, researchers are trying to use those anti-viral agents as a therapeutic regime for novel coronavirus disease 2019 [32-37]. As of now anti-viral drugs are used by several clinical and preclinical studies and awaiting for prospecting results after formal approvals from their respective institutes.

Some of the listed drugs are Chloroquine being most used for clinical trials, failover by Shenzhen, Guangdong province, ChAdOx1 nCoV-19 by University of Oxford Thames Valley Region, Gimsilumab by Roivant Sciences, AdCOVID by Altimmune with the University of Alabama at Birmingham (UAB), AT-100 (rhSP-D) by Airway Therapeutics INO-4800 as a novel coronavirus vaccine Inovio Pharmaceuticals and Beijing Advaccine Biotechnology, APN01 by University of British Columbia and APEIRON Biologics, mRNA-1273 vaccine by Moderna and Vaccine Research Center, Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine by MIGAL Research Institute, Brilacidin by Innovation Pharmaceuticals, CytoDyn by leronlimab, Remdesivir (GS-5734) by Gilead Sciences, Actemra by Roche, REGN3048-3051 and Kevzara by regeneron. Even then, till date of this review period none of them have been declared final with drug results.

6. RESULTS

6.1 Identification of Studies

Clinical studies done in coronavirus disease 2019, 369 articles were downloaded from two data bases namely, PubMed and Scopus. Then 38 duplicate articles were excluded and 331 articles were screened. Out of 331 articles, 168 papers were ineligible through abstract screening and left with 163 articles. Based on the exclusion criteria, 82 review articles, 51 articles not related to SARS-COV-2 and 4 articles not written in English, totally 137 articles were excluded. Eventually, 26 articles were reviewed with required parameters (Fig. 1).
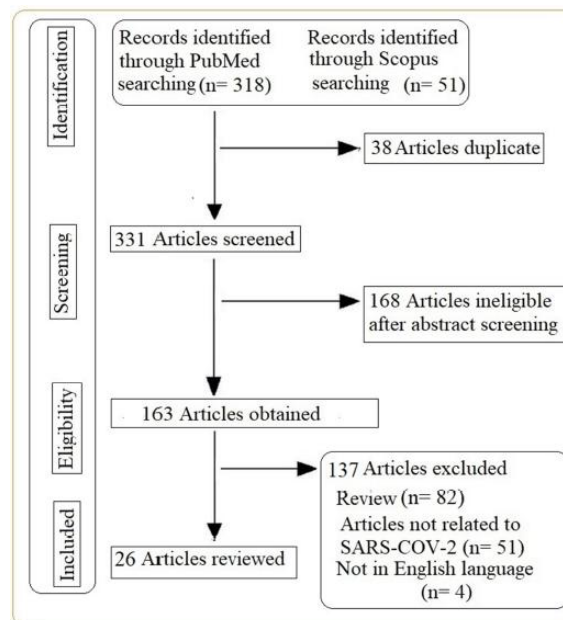

Fig. 1. Flow diagram of choosing the appropriated articles

Table 1. Titles of the completed clinical trials found in https://clinicaltrials.gov/ from January 12, 2020 to May 30, 2020 [31]

1. COVID-19 Endoscopy Survey (COVID-19 Endo)
2. An Investigation Into Beneficial Effects of Interferon Beta 1a, Compared to Interferon Beta 1b And The Base Therapeutic Regiment in Moderate to Severe COVID-19: A Randomized Clinical Trial
3. COVID-19 outbreak and solid organ transplantation (sot) : an international web based survey
4. Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure
5. Hypertension in Patients Hospitalized With COVID-19
6. Almitrine and COVID-19 Related Hypoxemia
7. Efficacy and Safety of Hydroxychloroquine for Treatment of COVID-19
8. Hydrogen/Oxygen Mixed Gas Inhalation for Coronavirus Disease 2019 (COVID-19)
9. Impact of COVID-19 on Psychological Status in Case of IVF Interrupted or Postponed
    SARS Cov-2 in Conjunctival Secretion
10. Baricitinib Therapy in COVID-19
11. Intravascular Access of COVID-19 Patient Under Personal Protective Equipment
12. COVID-19 Pandemic and Female Sexual Behavior
13. LDCT in COVID-19 Pneumonia: a Prospective Moscow Study
14. Prognostic Factors Keeping Track for COVID-19 Pneumonia
15. Impact of Swab Site and Sample Collector on Testing Sensitivity for COVID-19 Virus in Symptomatic Individuals
16. Predicting Death and ICU Admission in COVID-19 Patients in ED
17. Non-contact Endoscopy at Covid-19 Outbreak
18. Use of High Flow Nasal Cannula Oxygen and Covid-19 Acute Hypoxemic Respiratory Failure
19. Changes in Preference for Surgery of Patients Signed up for Arthroscopic Procedures
20. Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination form CoV Treatment
21. The Effects of Pulmonary Physiotherapy Treatments on Patients With COVID-19
22. Can the Prediction Market Improve Predictions of COVID-19?
23. D-dimer Levels in Pregnant With COVID-19
24. Hyperimmune Plasma for Critical Patients With COVID-19 (COV19-PLASMA)
25. An Observational Study of the Use of Siltuximab (SYLVANT) in Patients
26. Diagnosed With COVID-19 Infection Who Have Developed Serious Respiratory Complications (SISCO**)**
27. COVID-19 PCR Test Results in Asymptomatic Pregnants

Table 2. Study type, number of patients and sponsors of the clinical trials [31]

Study type	Number of patients	Age in Year	Sex	Study sponsor
Observational	163	30-70	Both	Al-Azhar University Cairo, Egypt
Randomized	60	18	Both	Shahid Beheshti University of Medical Sciences, Iran
Observational	1819	All	Both	Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Randomized	80	≥ 18	Both	Renmin Hospital of Wuhan University
Observational	275	18-100	Both	Zhenhua Zen, Hankou, Hubei, China
Observational	17	≥ 18	Both	Central Hospital, Nancy, France
Randomized	30	≥ 18	Both	Shanghai Public Health Clinical Center
Non- Randomized	90	18-75	Both	Guangzhou Institute of Respiratory Disease, China
Observational	503	≥ 18	F	Ospedale Policlinico San Martino, Italy
Observational	100	≥ 18	Both	Università degli Studi dell'Insubria, Italy
Non-Randomized	12	18-85	Both	Fabrizio Cantini, Italy
Randomized	41	≥ 18	Both	Poznan University of Medical Sciences, Poland
Observational	58	≥ 18	F	Acibadem University, Istanbul, Turkey
Non-Randomized	230	≥ 18	Both	Research and Practical Center of Medical Radiology, Moscow, Russia
Observational	198	18-100	Both	Catholic University of the Sacred Heart, Roma, Italy
Observational	533	All	Both	Bill and Melinda Gates Foundation, United States
Observational	300	≥ 18	Both	Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Interventional	5	18-80	Both	Changhai Hospital, Shanghai, China
Observational	62	≥ 18	Both	Hôpital Louis Mourier, France
Observational	79	≥ 18	Both	Region Zealand, Denmark
Randomized	127	≥ 18	Both	The University of Hong Kong
Randomized	40	18-75	All	Tehran University of Medical Sciences, Iran
Randomized	560	≥ 18	All	National University, Singapore
Observational	300	18-45	F	Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey
Interventional	49	≥ 18	All	Foundation IRCCS San Matteo Hospital, Italy
Observational	220	≥ 18	All	A.O. Ospedale Papa Giovanni XXIII. Italy
Observational	179	All	F	Istanbul Medipol University Hospital

Table 3. Intervention, intervention model, and sampling methods of the clinical trials [31]

Intervention Model	Intervention	Clinical trial registration No	Sampling method
Cohort	Other: Practice details Hydroxychloroquine	NCT04342637	Probability sampling N/A
Parallel assignment	Lopinavir / Ritonavir Interferon Beta-1A and Beta-1B	NCT04343768	
Survey group	Other: Survey Group	NCT04367896	Non- Probability sampling
Parallel assignment	Drug: methylprednisolone therapy , Standard care	NCT04244591	N/A
Case-control	N/A	NCT04318301	Probability sampling
Case-control	N/A	NCT04380727	Non- Probability sampling
Parallel assignment	Hydroxychloroquine	NCT04261517	N/A
Parallel assignment	Device: Hydrogen Oxygen Generator with Nebulizer •Other: Standard-of-care	NCT04378712	N/A
Cohort	Behavioral: Generalized Anxiety Disorder-7 (GAD-7)Patient Health Questionnaire-9(PHQ-9)	NCT04395755	Non- Probability sampling
Case-crossover	Diagnostic Test: Tears swab	NCT04402853	Probability sampling
Crossover assignment	Drug: Baricitinib 4 MG Oral Tablet	NCT04358614	N/A
Crossover assignment	Device: Intravenous access, •Device: Intraosseous access	NCT04366297	N/A
Cohort	Behavioral: fsfi survey	NCT04374422	Non- Probability sampling
Crossover assignment	Diagnostic Test: Low-dose Chest CT	NCT04379531	N/A
Case-control	N/A	NCT04324684	Non- Probability sampling
Case-control	Diagnostic Test: Testing Sensitivity forSARS-CoV-2 Virus in Symptomatic Individuals	NCT04321369	Non- Probability sampling
Cohort	N/A	NCT04371562	Non- Probability sampling
Single group assignment	Device: Non-contact MCE system	NCT04320953	N/A
Cohort	Device: patients receiving nasal high flow	NCT04385823	Non- Probability sampling
Cross-sectional	Behavioral: Change in preference to surgery under COVID-19 pandemic	NCT04370678	Non- Probability sampling
Parallel assignment	Drug: Lopinavir/ritonavir,: Ribavirin, Interferon Beta-1B	NCT04276688	N/A
Parallel Assignment	Other: Pulmonary Physiotherapy Techniques	NCT04357340	N/A
Parallel Assignment	Other: Prediction Market	NCT04410692	N/A
Case-Control	Other: Blood D-dimer assay	NCT04389554	Non-Probability Sample
Single Group assignment	Other: hyper immune plasma	NCT04321421	N/A
Cohort	N/A	NCT04322188	Non-Probability Sample
Case-Crossover	Diagnostic Test: Reverse transcription polymerase chain reaction	NCT04410939	Non-Probability Sample

Table 4. Clinical trials starting date, completion date, and place [31]

Study Starting Date	Study Completion Date	Place
April 10, 2020	May 1, 2020	Kings County Hospital Center, Brooklyn, NY, USA Faculty of Medicine, Zagazig University, Zagazig, Sharkia, Egypt Ahvaz Imam hospital, Ahvaz, Iran, Islamic Republic of Iran
April 9, 2020	April 27, 2020	Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran, Islamic Republic of Iran
March 24, 2020	April 27, 2020	Fondazione Policlinico Universitario "Agostino Gemelli", Rome, Italy
January 26, 2020	April 13,2020	Medical ICU,Peking Union Medical College Hospital, Beijing, Beijing, China
March 21, 2020	March 30, 2020	Hankou Hospital, Hankou, Hubei, China
March 20, 2020	April 25, 2020	Centre Hospitalier Universitaire NANCY, Vandoeuvre-les- Nancy, France
February 6, 2020	February 25, 2020	Shanghai Public Health Clinical Center, Shanghai, Shanghai, China
January 21, 2020	March 23, 2020	First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China
April 1, 2020	May 15, 2020	IRCCS Ospedale Policlinico San Martino, Genoa, Italy
February 1, 2020	May 20, 2020	ASST Sette Laghi, Varese, Italy
March 16, 2020	April 7, 2020	Fabrizio Cantini, Prato, Tuscany, Italy
January 12, 2020	February 25, 2020	Lazarski Univeristy, Warsaw, Poland
April 10, 2020	April 12, 2020	Haseki Training and Research Hospital, Istanbul, Turkey
April 25, 2020	May 22, 2020	Victor Gombolevskiy, Moscow, Russian Federation
March 31, 2020	May 7, 2020	Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
March 9, 2020	March 23, 2020	Everett Clinic, Seattle, Washington, United States
March 1, 2020	April 15, 2020	Marcello Covino, Roma, RM, Italy
March 16, 2020	April 9, 2020	Changhai Hospital, Shanghai, China
March 1, 2020	May 4, 2020	Hôpital Louis Mourier, Assistance Publique - Hôpitaux de Paris, Colombes, France
April 17, 2020	April 24, 2020	Zealand University Hospital, Køge, Zealand Region, Denmark
February 10, 2020	March 31, 2020	University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong
April 2, 2020	May 30, 2020	Imam Khomeini Hospital Complex, Tehran, Iran, Islamic Republic of Iran
May 15, 2020	May 17, 2020	National University of Singapore, Singapore, Singapore
May 14, 2020	May 29, 2020	Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turgut Ozal, Turkey
March 17, 2020	May 7, 2020	Catherine Klersy, Pavia, PV, and Ospedale Asst Carlo Poma Mantova, Italy
March 19, 2020	May 7, 2020	ASST - Papa Giovanni XXIII, Bergamo, Italy
April 10, 2020	May 21, 2020	Istanbul Medipol University, Istanbul, Turkey

Table 5. Primary outcome measures and secondary outcome measures of the clinical trials [31]

Primary Outcome Measures	Secondary Outcome Measures
Effect of GI societies recommendations on prevention of SARS-CoV-2 infection [Time Frame: 4- 6months] PDF 1	To measure the percentage change in performed endoscopic procedure in response to COVID-19 [Time Frame: 4- 6 months]
Time to clinical improvement [Time Frame: From date of randomization until 14 days later.]	Mortality [Time Frame: From date of randomization until 14 days later.] If the patient dies, we have reached an outcome.
Management of Solid Organ Transplant during COVID-19 pandemic [Time Frame: 20/04/2020]	Equity of resource distribution [Time Frame: 20/04/2020]
Lower Murray lung injury score [Time Frame: 7 days after randomization]	Lower Sequential Organ Failure Assessment (SOFA) score [Time Frame: 7 days after randomization]
Rate of Death [Time Frame: From date of admission until the date of death from any cause, up to 60 days]	The severity of pneumonia [Time Frame: From date of admission until the date of discharge or death from any cause, up to 60days]
Changes from baseline PaO2 (mmHg) [Time Frame: 45 minutes after Almitrine infusion] Partial pressure of oxygen in arterial blood	Changes from baseline PaO2 (mmHg) [Time Frame: 8 hours] partial pressure of oxygen in arterial blood
The virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3 [Time Frame: 3 days after randomization]	Number of participants with treatment-related adverse events as assessed by CTCAE v5.0 [Time Frame: 14 days after randomization]
The proportion of patients with improved disease severity at day 2 [Time Frame: from baseline to day 2]	The change from baseline in oxygen saturation at day 2. [Time Frame: from baseline to day 2]
Severity of anxiety [Time Frame: 1-4 weeks after communication of interrupted or delayed IVF]	N/A
Virus presence in COVID 19 patients tears [Time Frame: 1 day]	Concordance to Naso-Pharingeal Swab [Time Frame: 1 day]
To assess the safety of baricitinib combined with antiviral (lopinavir-ritonavir) in terms of serious or non-serious adverse events incidence rate. [Time Frame: 2 weeks]	To evaluate the impact of baricitinib in terms of clinical, laboratory, respiratory parameters. [Time Frame: 2 weeks]
Successful rate of first intravascular access attempt [Time Frame: 1 da]	Time to successful access [Time Frame: 1 day]
FSFI (Female Sexual Function Index) SCORE difference [Time Frame: 1 year]	N/A
Evaluate the correlation between standard CT and low-dose CT scans for the detection of community-acquired pneumonia. [Time Frame: Upon completion, up to 1 year]	Threshold value of the infiltration zone size detected by low-dose CT scan compared to standard CT scan. [Time Frame: Upon completion, up to 1 year]
Rate of recovery [Time Frame: 3 weeks]	Time to improvement [Time Frame: 3 weeks]
Accuracy of patient administered tests [Time Frame: 2 weeks]	N/A
7-day death [Time Frame: 7 day]	N/A
Technical success [Time Frame: During the procedure]	Clinical success [Time Frame: During the procedure]
Changes in ROX index [Time Frame: Up to 2 Months]	NHF failure [Time Frame : Up to 2 Months]
Change in preference [Time Frame: 3 months]	Change in preference between groups [Time Frame: 3 months]
Time to negative NPS [Time Frame: Up to 1 month]	Time to negative saliva [Time Frame: Up to 1 month]

Primary Outcome Measures	Secondary Outcome Measures
Mixed venous O2 pressure (PVO2) [Time Frame: Baseline]	Mortality rate [Time Frame: until one month]
Predictions of COVID-19 Cases and Deaths [Time Frame: 24hr	Fear [Time Frame: 24 hours]
Compare D-dimer values of COVID-19 patients and healthy pregnant women [Time Frame: one day]	N/A
Death [Time Frame: within 7 days]	Time to extubation [Time Frame: within 7 days]
Mortality in siltuximab treated patients [Time Frame: 30 days]	he need of invasive ventilation in siltuximab patients Reduction of the need of time of ventilator support [Time Frame: 30 days]
Rate of positive COVID-19 cases in asymptomatic pregnant women [Time Frame: 1 day]	N/A

6.2 Study Selection

The study selection criteria were based on prospective clinical characteristics and virological evaluation, diagnosis and clinical trial. Also only English written articles were included. The titles of the clinical trials (Table 1), study type, number of patients and sponsors (Table 2), intervention, intervention model and sampling methods (Table 3), clinical trials starting date, completion date and place details (Table 4), primary outcome measures and secondary outcome measures (Table 5) of the clinical trials are presented in respective order [31]. Of the completed human clinical trials obtained from https://clinicaltrials.gov/, the total patients who were included in the clinical trial were 6130. Out of 6130 patients, 1060 (17.29%) were only females whereas the rest of 5070 (82.71%) were both males and females.

Of the 6130 patients, 163 patients were 30-70 years old, 60 patients were 60 years old, 2531 patients were in all age groups and the rest 3376 patients were ≥ 18 years old. During the clinical trials, the researchers used four study types namely, observational study (14 studies), randomized study (8), non-randomized study (3) and interventional study (2). From twenty seven completed clinical trials conducted between January 12, 2020 to May 30, 2020, 8 studies were done and sponsored in Italy, 6 studies were done and sponsored in China, 3 studies were done and sponsored in Turkey, in Iran and France 4 studies were done and sponsored (2 study in each country), the rest 6 clinical trials were done and sponsored in Poland, USA, Russia, Denmark, Singapore, and Egypt (1 study in each country). For all the completed clinical trials in 11 countries, eight different interventional models were applied namely, cohort (6 studies), parallel assignment (7), case-control (5), case-cross-over (2), cross-over assignment (3), single group assignment (2), survey group (1) and cross-sectional (1). Out of completed clinical trials, 3 studies used probability sampling method and 12 studies used non-probability sampling method, for the rest 12 studies the sampling method was not mentioned. Interventional application of drugs, devices and other methods during the clinical trials are been listed in Table 3.

7. DISCUSSION

COVID-19 is one kind of coronaviruses categorized in the group of β-coronavirus clusters. It is a positive-stranded single-stranded RNA virus [38]. The current flare-up of coronavirus disease 2019 is creating considerable general wellbeing challenges globally. COVID-19 incites patient's immune responses which, when severe, harm the lungs and cause passing away of patient [39]. From the selected articles for the study undertaken following sub-titles are been discussed based on the need of the topic.

7.1 Depiction of Intercessions

Of now, no confirmed treatment is available for SARS-COV-2 [40]. To control the rise in COVID-19 pandemic, we depend on isolation, confinement and infection control measures to forestall feast of the disease [40] and on steady consideration including oxygen and mechanical ventilation for tainted patients. Today, various medications exist for time being evaluation of patients with SARS-COV-2 namely, remdesivir, drugs containing lopinavir and ritonavir, chloroquine phosphate or hydroxychloroquine, tocilizumab, corticosteroids, stem cells and different sorts of intercessions and many more [41]. Additional instances of possible interventions for the treatment of COVID-19 can be found in Table 3.

7.2 Diagnostic Specimens

The upper or lower respiratory tract are the places where specimen can be collected for diagnosis of COVID-19. The most appropriate specimen for the detection of the virus was sputum, trailed by nasal swabs and throat swabs [42]. In recently affirmed COVID-19 tainted patients, a meta-analysis of saliva testing and nasopharyngeal swab tests revealed the sensitivity result as 91% (95% CI = 80% - 99%) and 98% (95% CI = 89% -100%) for saliva and nasopharyngeal swab tests respectively with moderate heterogeneity among considers [43].

Another investigation indicated that saliva was the most befitting specimen for detecting the virus [44]. As the collection of the saliva sample is free from any pain it can likewise be considered for self-examining. In a circumstance where a nasopharyngeal or other previously mentioned sample aren't satisfactory, salivation could be considered as an elective specimen. The blend of nasopharyngeal/oropharyngeal swab tests have demonstrated progressively sensitive for diagnosis of COVID-19 contrasted with nasopharyngeal swab just in three distinct investigations [45]. Saliva would be the most

potential candidate specimen for ease of noninvasive specimen collection and testing unless limitations for accuracy, sensitivity, preciseness and test reliability.

7.3 Diagnostic Assays

The three most used assays are enzyme-linked-immunosorbent-assay (ELISA), chemiluminescence assay (CLIA) and lateral flow assay (LFA). Besides, virus neutralization tests are also used which can specifically detect neutralizing antibodies, but this is mainly used for assay validation and research. Preliminary reports on ELISA assays have shown a good correlation of antibody titration results with virus-neutralizing antibodies [46,47]. Apart from these main detection assays, whole-genome sequencing can also be performed to determine the sequence of the virus in the sample with possible quasi-species variants [48]. Even then, most of the studies report as nucleic acid test, viral test and antibody test as diagnosis and confirmation of the subjected sample.

7.4 Diagnostic Accuracy and Validation

In vitro diagnostic medical devices (IVDs) commission has made a working report available in open access journals which proposes a conditional meaning of COVID-19 diagnostic test execution standards and has checked on publicly accessible information concerning the capability of CE-marked commercial IVD tests [49]. Analytical sensitivity, analytical specificity, clinical sensitivity and clinical specificity were the key points incorporated in the criteria. As a follow-up of this record, the European Commission is ordering an accessible database, the company's information about CE-marked commercial IVD tests and investigating in-house research facility created tests with execution information in scientific publications [50]. Experts from WHO reports that it is suitable to procure Emergency Use Listing procedure (EUL) and shortlisting of molecular detection assays on the basis of data from manufacture for full clinical validation and pre-qualification is required.

7.5 Ongoing Clinical Trials Results

The previous research of the *In vitro* and *In vivo* experiments indicates that remdesivir has antiviral effect against various types of coronaviruses such as SARS-CoV and MERS-CoV [51,52]. The recent *In vitro* study showed remdesivir can block the replication of SARSCoV- 2. Hence, this drug is being tested in many clinical trials in various countries, embracing two randomized phase III trials in China (NCT 252664 and NCT 04257656) [53]. Looking into the promising result obtained from the clinical trials done in favipiravir, the National Medical Products Administration of China permitted favipiravir is the first anti-SARS-CoV-2 drug in China in March 2020 [54]. Regarding Ivermectin, the recent *In vivo* experiment has demonstrated Ivermectin's ability to decrease viral RNA up to 5,000 fold after two days of infection with COVID-19 [55]. The combination of lopinavir and ritonavir clinical trial done against SARS-CoV-2 patients with slight and moderate coronavirus disease 2019 (NCT 04252885) exhibited low positive effect for improving the clinical outcome [52]. The current study noted that there is no indication of clinical importance for patients who took hydroxychloroquine/Azithromycin as therapeutic regime hence; wider randomized controlled trials are required for additional assessment [56].

7.6 Vaccine

There is a huge worldwide exertion to prepare vaccine for assurance against COVID-19 and in a minimum of ten vaccine candidates have starting at early June 2020 entered clinical trials, including stage II trials [57]. Protection and immunogenicity information has been stated in the scientific publication for the first-in-human trial evaluating a vector-based COVID-19 vaccine candidate led in China and needs additional research [58]. The European Medicines Agency (EMA) has been in conversation with researchers of 33 possible COVID- 19 vaccines since May 26, 2020. Nevertheless, the EMA supposes that it might take a minimum of one year before the vaccine is affirmed and accessible for boundless use in the EU/EEA [59]. The chances and difficulties of preparing vaccines against SARS-COV-2 are talked in detail [60] and the valuable experience from SARS-CoV-1 vaccine advancement may help to develop COVID-19 vaccine design, testing and execution [61]. Currently, no treatment has exhibited effective protection of SARS-COV-2. Short time to rigorously sick patients need steady consideration and oxygen supplementation. Possible medicines ought to be prudently evaluated in randomized controlled trials (RCTs) prognosis. Many large-scale multicenter trials are in progress to utilize a properly strong approach for appraisal of possible therapeutics, such as "WHO Solidarity

Trial, a few United States National Institutes of Health and national trials in the numerous EU Member States." [62,63]. Enrolment of patients in clinical trials should be encouraged. Remdesivir, interferon β-1a the combination of lopinavir/ritonavir, hydroxychloroquine, interleukin-6 (IL-6) and IL-4 are the possible drugs undergoing in clinical trials to evaluate the possible side-effects and effectiveness to use as the medication of SARS-COV-2 [64].

From the analysis, it is noted that 172 countries and several candidate vaccines are deeply engrossed in COVID-19 vaccine portfolio - COVAX – a world largest and most diverse COVID-19 vaccine. COVAX, under the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator, is co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, the Vaccine Alliance, and the World Health Organization (WHO) – in partnership with vaccine manufacturers of developed and developing country. Mass vaccination programme begun for the first instance in December 2020 with issuance of Emergency Use Listing (EULs) for BNT162b2 (COVID-19 vaccine by Pfizer) by WHO. Up till 15 February 2021, administration of 175.3 million vaccines has been done. On the same day, WHO issued EULs for two more versions - AstraZeneca/Oxford - COVID-19 vaccines manufactured by Serum Institute of India and SKBio. Tracking on EULs for other vaccines till June, products and progress about regulatory review with regular updates are been done by WHO.

8. CONCLUSION

COVID-19 can cause a conceivably deadly infection in humans and most usually reported known clinical manifestations of patients with coronavirus disease in 2019 were fever, cough, and expectoration. Attachment of the virus to the surface receptor of target cells and the fusion of viral and host membranes are the two consecutive steps that the virus uses to cause infection in humans. Knowing the way to enter the cell and the mechanism to escape the immune system can be the potential targets to develop a novel SARS-COV-2 treatment protocol. This could be the reason for testing the clinical trials with varied age grouped individuals majority with ≥ 18 years old, followed by overall ages, less numbered with 30-70 years old and significant studies were reporting only with females. With the pace of spread and

development of the COVID-19 pandemic across the globe and the possible developments for combating the virus, safely awaiting following the existing control measures is only the safe route. The most awaited results for overcoming the COVID-19 pandemic are safer diagnostic testing sample without invasion or discomfort for patients, easier, quicker and sensitive diagnostic test for both testing and confirmation of subject and finally the curable vaccine to fight back the infection due to COVID-19 virus. Probably by the end of this 2021 a better solution to manage the COVID-19 virus infection will be found and will end up with COVID-19 virus free world with a message to equip the future with required medical advanced tools.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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