Experimental studies on COVID-19: overview of the world scientific production

Estudos experimentais sobre COVID-19: panorama da produção científica mundial

Estudios experimentales sobre COVID-19: panorama de la producción científica mundial

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Abstract

Objective: To describe the world panorama of the production of experimental studies on COVID-19.

Methods: Descriptive study conducted in April 2020, based on a search for clinical trial records on the Clinical Trials and Brazilian Clinical Trials Records portals. The statistical analysis was descriptive.

Results: Of the 645 clinical trials in the sample, there was a predominance of 199 (30.9%) from Europe, 213 (33%) performed by hospital institutions, 482 (74.7%) with the objective aimed at the treatment. As for interventions surveyed, 394 (61.1%) were on drugs; 70 (10.8%) investigated biological interventions; 45 (7.0%) interventions with blood and blood products; 40 (6.2%), behavioral interventions; 38 (5.9%), interventions with equipment; 31 (4.8%), care/procedural interventions; 18 (2.8%), diagnostic interventions and nine (1.4%) dietary supplementation interventions. The studied population was composed of adult and elderly subjects in 515 (79.8%) studies, 635 (98.4%) investigated both sexes, the design of 480 (74.4%) included randomization, of 482 (74.7%) parallel allocation of participants and 373 (57.8%) did not have blinding.

Conclusion: The experimental studies on COVID-19 originated from Europe, were conducted by hospitals, on treatment in adult and elderly subjects, with randomization but without blinding. The findings may direct the performance of studies addressing the identified gaps.

Resumo

Objetivo: Descrever o panorama mundial da produção de estudos experimentais relacionados à COVID-19.

Métodos: Estudo descritivo, realizado em abril de 2020, a partir de busca pelos registros de ensaios clínicos, nos portais *Clinical Trials* e Registros Brasileiros de Ensaios Clínicos. A análise estatística foi descritiva.

Resultados: Dos 645 ensaios clínicos da amostra, houve predominância de 199 (30,9%) oriundos da Europa, 213 (33%) realizados por instituições hospitalares, 482 (74,7%) com objetivo direcionado ao tratamento. Quanto às intervenções pesquisadas, 394 (61,1%) foram sobre medicamentos; 70 (10,8%) investigaram intervenções biológicas; 45 (7,0%), intervenções com sangue e derivados; 40 (6,2%), intervenções comportamentais; 38 (5,9%), intervenções com equipamentos; 31(4,8%), intervenções assistenciais/procedimentais; 18 (2,8%), intervenções para diagnóstico e nove (1,4%), intervenções de suplementação dietética. Observou-se que, em 515 (79,8%) a população estudada foi composta por adultos e idosos, 635 (98,4%) investigaram ambos os sexos, o delineamento de 480 (74,4%) incluiu randomização, de 482 (74,7%) alocação paralela dos participantes e 373 (57,8%) não possuíu o cegamento.

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Conclusão: Os estudos experimentais sobre a COVID-19 foram oriundos da Europa, realizados por hospitais, sobre o tratamento em adultos e idosos, com randomização, mas sem cegamento. Os achados podem direcionar a realização de estudos, para contemplarem as lacunas identificadas.

Resumen

Objetivo: Describir el panorama mundial de la producción de estudios experimentales relacionados con la COVID-19.

Métodos: Estudio descriptivo, realizado en abril de 2020, a partir de la búsqueda de registros de ensayos clínicos en los portales *Clinical Trials* y Registros Brasileiros de Ensaios Clínicos. El análisis estadístico fue descriptivo.

Resultados: De los 645 ensayos clínicos de la muestra, hubo predominancia de 199 (30,9 %) oriundos de Europa, 213 (33 %) realizados por instituciones hospitalarias, 482 (74,7 %) con objetivo orientado al tratamiento. Respecto a las intervenciones investigadas, 394 (61,1 %) fueron sobre medicamentos; 70 (10,8 %) investigaron intervenciones biológicas; 45 (7,0 %), intervenciones con sangre y derivados; 40 (6,2 %), intervenciones de comportamiento; 38 (5,9 %), intervenciones con equipos; 31 (4,8 %), intervenciones asistenciales/procedimentales; 18 (2,8 %), intervenciones para diagnóstico, y 9 (1,4 %), intervenciones de suplementos dietéticos. Se observó que en 515 ensayos (79,8 %) la población estudiada fue compuesta por adultos y ancianos, en 635 (98,4 %) se investigaron ambos sexos, el diseño de 480 (74,4 %) incluyó aleatorización, de 482 (74,7 %) asignación paralela de los participantes y 373 (57,8 %) no poseían cegamiento.

Conclusión: Los estudios experimentales sobre la COVID-19 fueron oriundos de Europa, realizados por hospitales, sobre el tratamiento en adultos y ancianos, con aleatorización, pero sin cegamiento. Los resultados pueden orientar la realización de estudios que contemplen los vacíos identificados.

Introduction

The disease caused by the human coronavirus SARS-CoV-2 (COVID-19) was declared a pandemic in 2020. In May 2020, there were 5,404,512 cases and 343,514 deaths distributed in 212 countries.[1]

The COVID-19 outbreak represents a challenge for the public health system in the search for strategies that reduce the clinical threat to the population.[2] It is relevant to obtain greater knowledge about SARS-CoV-2[2,3] from large-scale clinical trials[3] for the optimization of actions to combat the pandemic and because information about the disease remains limited.

There is still no robust scientific content to support specific therapeutic protocols or vaccines, and several experimental studies are under development to assess the effectiveness of treatment options.[4,5] In this context, the results of experimental research have a potential role to guide the planning of effective interventions, thereby changing the exponential design of the epidemic path.

Chances of a safer and more effective health care during the pandemic are higher if supported by evidence-based results. It is important that these results present the evidence synthesized descriptively for consultation by health professionals. Such a presentation will enable the identification of little explored topics in research and methods not yet covered by existing studies. Thus, the non-explored themes and methods may be the target of future studies in order to contribute to the state of the art on this subject.

The objective of this study was to describe the world panorama of the production of experimental studies related to COVID-19.

Methods

This is a descriptive, quantitative study conducted in April 2020, in two online clinical trial portals: the Clinical Trials (www.clinicaltrials.gov), administered by the National Institutes of Health in the United States, is the largest clinical trial portal; and the Brazilian Registry of Clinical Trials (ReBEC) portal, available at http://www.ensaiosclinicos.gov.br/. The search in both portals was conducted using the descriptor "COVID-19" in the topic *condition* or *disease*, accessible from the Medical Subject Headings (MeSH).

The selection criteria were publications from 2020, without language delimitation, addressing experimental studies on COVID-19. Duplicate studies or those with interrupted or canceled status were excluded.

From the search, 1,093 records of clinical trials were found, of which 448 were excluded and 645 comprised the sample. Figure 1 shows the study selection flowchart.

A structured instrument, based on the Consolidated Standards of Reporting Trials - Consort 2010, was used for data collection. The

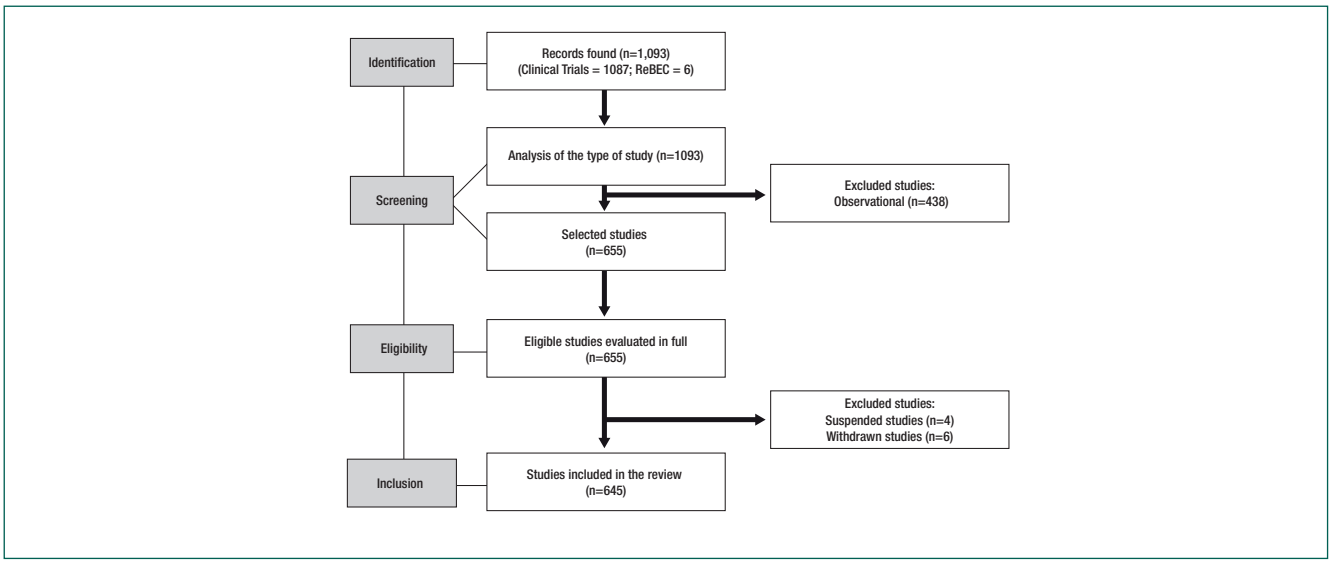

Figure 1. Flowchart of selection of studies

variables of interest were: country, study population, eligibility criteria for participants (age, sex), topic, sample size, type of randomization and blinding, allocation, type of intervention, duration of collection and additional information available in the record.

Each record was accessed on the portals for the collection of variables of interest with aid of the aforementioned instrument. After collection of all records, variables such as age, sample size, study duration and country were categorized in order to make the presentation of results more objective.

Data were tabulated in the Microsoft Excel 2010 software and analyzed statistically using the Statistical Package for the Social Sciences (SPSS), version 24.0. The results were presented descriptively with absolute and relative frequencies. The study complied with ethical principles in research and there was no need for approval by the Research Ethics Committee, since it was conducted with public domain data.

Results

Of the 645 clinical trial records analyzed, 199 (30.9%) were from Europe, 178 (27.6%) from North America, 111 (17.2%) did not have such information available, 109 (16.9 %) from Asia, 29 (4.5%) from South America, 18 (2.8%) from Africa and one (0.2%) from Oceania. Regarding the institution, 213 (33%) had collaboration from a hospital; 200 (31.0%) of universities; 146 (22.6%) from university hospitals and 86 (13.3%) from the pharmaceutical industry.

With regard to the status of recruitment, 328 (50.9%) clinical trials had not started it, 277 (42.9%) had started it, 24 (3.7%) were in the process of sending the invitation and 16 (2.5%) had completed the recruitment. In relation to the objective, 482 (74.7%) were about treatment; 87 (13.5%) on prevention; 20 (3.1%) contemplated supportive care; 16 (2.5%), the diagnosis; seven (1.1%) were studies on health services; five (0.8%) on screening and five (0.8%) were basic research.

The collection time of 306 (47.4%) studies was up to six months; in 187 (29.0%), it was seven to 12 months; in 110 (17.1%), from one to two years and in 42 (6.5%), it was more than three years. The sample size had a minimum of four and a maximum of 55,000 participants, with an average of 681.81 (±3,083.150) and median of 144 (interquartile range = 54,996). The minimum age of study participants was six months and the maximum age was 104 years. The characterization of clinical trials regarding the topic addressed, randomization, type of allocation in the intervention, blinding, sample size

and profile of participants (sex and life cycle) is detailed in table 1.

Table 1. Characterization of methodological aspects of clinical trials on COVID-19

Variables	n(%)
Subjects	
Drug treatment	394(61.1)
Biological interventions	70(10.8)
Blood and blood products	45(7.0)
Behavioral Interventions	40(6.2)
Use of equipment	38(5.9)
Care procedures	31(4.8)
Diagnostic tests	18(2.8)
Dietary supplementation	9(1.4)
Randomization	
Randomized	480(74.4)
Non-randomized	56(8.7)
Not informed	109(16.9)
Allocation in therapeutic intervention	
Parallel assignment	482(74.7)
Single group assignment	124(19.2)
Sequential assignment	18(2.8)
Crossover assignment	12(1.9)
Factorial assignment	9(1.4)
Blinding	
Open	373(57.8)
Single	74(11.5)
Double	59(9.1)
Triple	46(7.1)
Quadruple	93(14.4)
Sample size	
1 to 100	269(41.7)
101 to 500	251(38.9)
501 to 999	46(7.1)
Above 1,000	79(12.2)
Sex of interest	
Both	635(98.4)
Female only	9(1.4)
Male only	1(0.2)
Life cycle of participants	
Children and adolescents	3(0.5)
Adolescents, adults and the elderly	16(2.5)
Adults only	56(8.7)
Old adults and elderly	7(1.1)
Adults and elderly	515(79.8)
Elderly only	14(2.2)
The whole life cycle	34(5.3)

Only 6.8% (44) of studies were classified as phase 4, that is, those that already have a marketing authorization. Most were recruiting (n=16; 36.4%) or not recruiting participants (n=22; 50%). These studies were focused on drug treatment (n=41; 93.2%), biological interventions (n=2; 4.5%) and dietary supplementation (n=1; 2.3%). The main interventions were the use of chloroquine or hydroxychloroquine (n=17; 38.6%), anticoagulants such as enoxaparin (n=2; 4.5%) and use of the BCG vaccine to prevent COVID-19 (n=2; 4.5%).

Employees were hospital institutions or universities, each representing 40.9% (18), mainly from Europe (n=21; 47.7%) or North America (n=10; 22.7%). The target audience were adult or elderly subjects (n=36; 81.8%) of both sexes (n=44; 100%). Regarding methodological characteristics of these experimental studies, there was a predominance of samples with between one and 100 participants (n=20; 45.5%) or 101 and 500 (n=15; 34.1%). Most studies had parallel assignment, in which two or more groups of participants received different medications (n=32; 72.7%) and 56.8% (25) were classified as open trials.

The use of 206 drugs was identified in 394 experimental studies. There was a prevalence of hydroxychloroquine in 78 (19.76%) studies, hydroxychloroquine combined with azithromycin in 31 (7.85%), combination of lopinavir and ritonavir in 23 (5.8%), azithromycin in 19 (4.8%), chloroquine in 16 (4%), tocilizumab in 14 (3.5%) and ascorbic acid in 12 (3.0%). Of the 125 studies involving the use of chloroquine or hydroxychloroquine, 40% (50) were phase 2 clinical trials with predominance of samples of between 101 and 500 participants (n=51; 40.8%), randomized (n=114; 91.2%) and open (n=59; 47.2%). The other medications varied, for example; favipiravir, colchicine, methylprednisolone, ruxolitinib, baricitinib, sarilumab, anakinra, nitazoxanide and remdesivir.

With regard to biological interventions, most contemplated the use of humanized monoclonal antibodies, whereas, in interventions with blood and derivatives, convalescent plasma was the most used. Regarding diagnostic interventions, the identification of COVID-19 serology was the most

Table 2. Distribution of biological interventions with blood and derivatives and interventions for diagnosis investigated in clinical trials on COVID-19

Variables	n(%)
Biological interventions (n = 70)	
Use of humanized monoclonal antibody	25(35.7)
Use of stem cells	20(28.6)
Use of vaccine to prevent COVID-19	14(20.0)
NK cell transfer	4(5.8)
Bacterial suspension	2(2.9)
Ozone autohemotherapy	1(1.4)
Biological samples for phenotype/genotype correlation	1(1.4)
Human amniotic fluid	1(1.4)
Genome sequencing	1(1.4)
Use of anti-interferon antibody	1(1.4)
Interventions with blood and blood products (n = 45)	
Use of convalescent plasma	32(71.2)
Blood collection to evaluate COVID-19 biomarkers	4(8.9)
Blood collection to assess immune response	2(4.5)
Blood collection to assess hyperactivity of the renin-angiotensin system	1(2.2)
Blood collection to assess hypercoagulation	1(2.2)
Blood collection to evaluate seroconversion of healthcare workers	1(2.2)
Blood sample collection to identify C5a receptor expression	1(2.2)
Blood sample collection to identify neuromarkers	1(2.2)
Use of hyperimmune plasma	1(2.2)
Blood collection to evaluate cardiovascular and renal biomarkers	1(2.2)
Diagnostic interventions (n = 18)	
COVID-19 serology	5(27.8)
PCR testing	2(11.1)
Comparison between tests	2(11.1)
COVID-19 rapid test	2(11.1)
Salivary test	2(11.1)
Cytokine dosage	1(5.6)
Sensitivity and specificity between tests	1(5.6)
Conjunctival cell swab	1(5.6)
Rhinopharynx swab	1(5.6)
Lung ultrasound	1(5.6)

NK – Natural Killer; PCR – Reverse-transcriptase Polymerase Chain Reaction

Table 3. Distribution of interventions with equipment and care/procedural interventions investigated in clinical trials on COVID-19

Variables	n(%)
Interventions with equipment (n = 38)	
Devices for oxygen therap)*	12(31.7)
Devices for vascular procedures†	8(21.2)
Surgical masks and N95	3(7.9)
Sensor for monitoring vital signs	2(5.5)
Telerehabilitation platform after hospitalization	1(2.6)
Algorithm for identification of COVID-19	1(2.6)
Barrier enclosure during the endoscopy	1(2.6)
Barrier box during intubation	1(2.6)
Calorimetry in people with COVID-19	1(2.6)
Vest for transthoracic VQ manipulation	1(2.6)
Mouthwash	1(2.6)
Vagus nerve stimulation	1(2.6)
Artificial intelligence in ultrasound	1(2.6)
Swab prototype	1(2.6)
Extracorporeal carbon dioxide removal	1(2.6)
Oral/nasal spray	1(2.6)
Local thermotherapy	1(2.6)
Care/procedural interventions (n = 31)	
Prone positioning	9(29.2)
Mechanical ventilation	3(9.8)
Pulmonary physiotherapy	2(6.6)
Blood collection to evaluate domestic transmission	1(3.2)
Echo doppler for deep venous thrombosis screening	1(3.2)
Prehospital intubation	1(3.2)
Evaluation of the patient after deep venous thrombosis	1(3.2)
Nasal saline irrigation	1(3.2)
Alveolar recruitment maneuver	1(3.2)
Auricular vagus nerve neuromodulation	1(3.2)
Early extracorporeal membrane oxygenation (ECMO)	1(3.2)
Ozone therapy	1(3.2)
Pulmonary rehabilitation	1(3.2)
Computed tomography with minimally invasive autopsy	1(3.2)
Cellular stromal vascular fraction self-implanted intravenously	1(3.2)
Hyperbaric oxygen therapy	1(3.2)
Oxygen therapy in home isolation	1(3.2)
Multiplex polymerase chain reaction (PCR)	1(3.2)
Low dose radiation	1(3.2)
Automated oxygen control	1(3.2)

*Hyperbaric chamber, oxygenation valve, respiratory training devices, automated compressor for mechanical ventilation, laryngoscope, positive airway pressure (PAP), hydrogen/oxygen generator with nebulizer, nebulizers and high flow nasal cannula; †Cytokine blood adsorber, intravascular access, hemofilter for extracorporeal membrane, plasma adsorber, leukocyte modulator

prevalent. The details of biological interventions with blood and derivatives and interventions for diagnosis are shown in table 2.

Thirty-one interventions involving the use/testing of equipment and 22 interventions of care/procedural nature were found. Prone positioning was the main care intervention (Table 3).

Interventions for dietary supplementation were observed in nine (1.4%) clinical trials, of which five (55.6%) addressed the use of vitamins C and D and zinc; and interventions by ketogenic diet aimed at intubated patients, use of prototypes, use of natural honey and antioxidants were each addressed in a study (11.1%). The most frequent behavioral interventions were related to the use of telemedicine for home monitoring, online psychosocial support and educational videos offering physical exercise guidance (Table 4).

Table 4. Distribution of behavioral interventions in clinical trials on COVID-19

Variables	n(%)
Behavioral Interventions (n = 40)	
Home monitoring (telemedicine)	7(17.5)
Online psychosocial support	3(7.5)
Educational video on physical exercises	3(7.5)
Meditation application	2(5.0)
Online stress support program	2(5.0)
Mindfulness online session	2(5.0)
Online session of cognitive behavioral therapy	2(5.0)
Online yoga session	2(5.0)
Health education to combat COVID-19	1(2.5)
Guidance on healthy meals	1(2.5)
Support program for people with scleroderma during the pandemic	1(2.5)
Support program for people with lupus during the pandemic	1(2.5)
Phobic fear screening	1(2.5)
Screening of postpartum women and their postpartum experiences	1(2.5)
Blood donor recruitment	1(2.5)
Individualized Ayurveda session	1(2.5)
Tele-intervention for diabetes management	1(2.5)
Tele-rehabilitation with physical exercises for the elderly	1(2.5)
Tele-rehabilitation with exercises for people with COVID-19	1(2.5)
Counseling Therapy by Automated Messaging Software	1(2.5)
Telephone-based screening and management of the population	1(2.5)
Use of prayer in ICU patients	1(2.5)
Use of telemedicine	1(2.5)
Psychoeducational video on stress control	1(2.5)
Financial advice	1(2.5)

ICU – Intensive Care Unit

Discussion

In this study, most experiments were randomized with parallel allocation. This is a relevant finding, because the reliability of the cause-effect relationship of clinical trials is associated with the comparison of groups, and the random allocation of participants to the groups contributes to a greater chance of homogeneity among participants in relation to characteristics that could lead to bias in the results.[6] In the pandemic scenario, trials with these characteristics helped to understand the effects of therapeutic interventions in different outcomes.

Another characteristic seen in clinical trials is blinding, although it was absent in most experiments. This is a noteworthy fact, considering that blinding consists of ignorance regarding the allocation of each participant, which can apply to participants themselves and/or members of the research team.[7] Such ignorance (blinding) contributes to avoid the emergence, measurement or overestimation of the observed effects. Participants may believe and refer to an improvement or worsening not consistent with reality if they know they are in the group that received a given intervention. In line with this reasoning, researchers can involuntarily have biased measurement inclined towards the results they aim to find, if they are aware of the group that participants belong to.[7]

This situation is aggravated when considering that blinding is one of the criteria evaluated for the inclusion of clinical trials in systematic reviews.[8] Thus, the large number of experiments on COVID-19 without blinding may constitute a relevant barrier for the development of systematic reviews and meta-analyzes on the topic. As meta-analyzes guide the decision of conducts to be incorporated into clinical practice, they are important for coping with the pandemic.

Most studies had not started recruiting participants to test interventions in clinical trials. This is an understandable fact, since the start of recruitment depends on steps inherent to the performance of the study, such as project design, ethical authorizations and funding.[9] Despite the importance of the prompt provision of scientific evidence in the pandemic context, it is relevant to follow such steps because they reflect on the quality of results obtained.

The target audience of the interventions was mostly composed of adult and elderly subjects. Systematic reviews showed evidence that people over the age of 65 with COVID-19 had a higher risk of worsening and death and that the disease had a milder course and better prognosis in children than in adults.[10,11] In a study conducted in China, the clinical characteristics of a group of elderly and of a group of young and middle-aged adult patients with COVID-19 were compared, and a higher mortality was identified among the elderly.[12] This evidence justifies the importance of conducting experimental studies with this population, since they are the most affected by the infection and more prone to the worst outcomes.

The subject investigated in more than half of clinical trials was related to drug treatment, and hydroxychloroquine was the most investigated

drug. This finding can be justified, because this is a low cost, widely used drug against malaria, which would enable its wide use to face the pandemic, in addition to having proven effective to control the COVID-19 infection invitro.[13] However, results from two meta-analyzes indicated no safety for its clinical use, since it has no benefits and increases the risk of adverse events and mortality in patients with COVID-19.[14,15]

Among the studies using biological interventions, a higher frequency of the use of human monoclonal antibody was observed. This is the main class of biotherapeutics for passive immunotherapy to combat viral infection and has been recognized as a potential treatment for many diseases.[16] Promising results in the use of monoclonal antibodies to treat other forms of coronavirus (MERS-CoV and SARS-CoV) that generated epidemics and deaths in different countries have motivated researchers to develop immunotherapy based on the association of monoclonal antibodies for COVID-19.[17]

Convalescent plasma interventions were the most used among experimental studies with blood and derivatives. The use of convalescent plasma has a positive history in the treatment of other viral infections such as pandemic influenza A (H1N1), avian influenza A (H5N1) and hemorrhagic fevers such as Ebola.[18] This treatment has been tested in the COVID-19 pandemic context and a series of cases have shown that patients with severe respiratory failure who received this intervention showed an increase in neutralizing antibodies and clinical improvements.[19] However, available studies on this type of treatment have low level of evidence and the development of experimental studies to clarify its effects is recommended.

Among the experimental studies on the diagnosis of COVID-19, interventions with the use of serology prevailed. The outbreak of SARS-CoV-2 infections required that countries used resources to increase the mass testing of the population, thereby increasing the demands for production of diagnostic tests.[20] In addition to direct tests through the use of rhinopharynx swab (RT-PCR), serological immunoassays integrated the diagnostic techniques;[21] hence the relevance of producing experimental studies of serological diagnoses for COVID-19.

When considering the importance of nutrition in the recovery of COVID-19, most clinical trials addressing this aspect investigated the supplementation of vitamins C and D and zinc. Investigations with this perspective are pertinent, since most infected patients present severe inflammation and anorexia at hospital admission, and the possibility of supplementation with these micronutrients is likely to contribute to the modulation of immune function and reduce the risk of infection.[22,23]

Regarding interventions with the use of equipment, there was a predominance of those related to the respiratory and blood systems. This result is expected, since the diagnosis and treatment of this disease involves the use of different devices, especially for blood collection/analysis and oxygen therapy.[24,25] Thus, when considering the systemic consequences of COVID-19, studies attesting the applicability and effectiveness of the use of these equipment are relevant.

Assistance to critically ill patients with COVID-19 involves care to maintain the respiratory system functions. Among assistance care, the therapy of implementation of prone positioning to improve the pulmonary efficiency of patients stood out. A meta-analysis that sought evidence of the application of this position indicated that pronation can decrease mortality in patients with severe acute respiratory syndrome when applied in the first hours of hospitalization of patients with impaired oxygenation.[26] Thus, the investigation of the effects of implementing this position, the best way to perform it and the frequency of use should be the target of further experimental studies to contribute to evidence-based practice of professionals who perform it.

Regarding behavioral interventions, there was a predominance of home monitoring by telemedicine. Such investigations may have been motivated by recommendations for professional follow-up without physical approach or the need to move patients to health institutions. Furthermore, telemedicine becomes an important strategy, given the increasing number of cases of SARS-CoV-2 contamination with a growing demand for a pre-clinical approach, care support and consultation.[27,28]

In this sense, the choice of the technology can be made through researches demonstrating the results of its use.

The limitation of the study is the possibility of not including clinical trials that were not registered in the researched portals. However, the investigated portals have wide registration adhesion in the Brazilian reality and mainly internationally, which is corroborated by the number of trials found and analyzed in the present study.

The contribution of this study is the identification of gaps related to the themes, methodological characteristics and geographical locations of clinical trials, which can motivate and direct the development of studies aimed to fill these gaps. In addition, by presenting the description of studies in progress, it is possible to determine the trend of the next publications of experimental studies, which may be of interest to health professionals and researchers.

Conclusion

The global panorama of the production of clinical trials on COVID-19 has a predominance of studies conducted by hospital institutions, originating in Europe, in which the recruitment of participants that has not yet started, objective directed to the treatment, and studied population composed of adult and elderly subjects of both sexes. The design of most studies included randomization and parallel allocation of participants, but did not have blinding. The most studied interventions were about drug treatment; besides these, biological interventions, with blood and derivatives, use of equipment, care procedures, diagnostic tests, dietary supplementation and behavioral interventions were tested. The most studied medication was hydroxychloroquine; the most studied biological intervention was with monoclonal antibody; the most researched intervention with blood and derivatives was with convalescent plasma; the diagnostic intervention was by serology; the most studied equipment were those aimed at the respiratory and blood systems; the most targeted care procedure in the experiments was prone positioning; the nutritional intervention was supplementation of Vitamins C and D and Zinc; and the most studied behavioral intervention was home monitoring by telemedicine. In order to provide scientific evidence that supports clinical decisions and contributes to the advancement of knowledge about COVID-19, is recommended the development of studies addressing the identified gaps related to research in the context of America, Asia, Africa and Oceania; performed with newborns, children and adolescents; investigating prevention, diagnosis, rehabilitation and aspects related to mental health; and including blinding in the methodological design.

Collaborations

Barros LM participated in the conception and design, data collection and interpretation, writing of the article, relevant critical review of the intellectual content and final approval of the version to be published. Galindo Neto NM and Sá GGM participated in the analysis and interpretation of data, writing of the article, relevant critical review of the intellectual content and final approval of the version to be published. Pereira JCN, Pereira JCN, Barbosa LU, Oliveira Neto JGO, Henriques AHB and Caetano JÁ participated in the relevant critical review of the intellectual content and final approval of the version to be published and agreed with all aspects of the manuscript in terms of veracity or integrity of information.

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