

Systematic Review Protocol: Main Clinical Variables for the COVID-19 Patients' Management at the Comprehensive Health Care in Brazil

Estael Luzia Coelho da Cruz-Cazarim¹, Pâmela Santos Azevedo², Adrielle Pereira Cordeiro³, Maiara Silva Araújo³, Damaris Salgueiro da Silva³, Matheus José Novais Landim³, Bárbara Caneschi da Costa³, Isadora Alhadas Oliveira Gomes³, Ana Karolina Toledo Fagundes³, Altacílio Aparecido Nunes⁴, Marina Morgado Garcia², Marcelo da Silva Silvério⁵, Alessandra Ésther de Mendonça⁵ & Maurilio de Souza Cazarim^{5*}

¹*School of Pharmaceutical Sciences of Ribeirao Preto, University of Sao Paulo, Brazil*

²*School of Pharmacy, Federal University of Minas Gerais, Brazil*

³*School of Pharmacy, Federal University of Juiz de Fora, Brazil*

⁴*Department of Social Medicine of Ribeirão Preto Medical School, University of Sao Paulo, Brazil*

⁵*Department of Pharmaceutical Sciences, School of Pharmacy, Federal University of Juiz de Fora, Brazil*

***Correspondence to:** Dr. Maurilio de Souza Cazarim, Department of Pharmaceutical Sciences, School of Pharmacy, Federal University of Juiz de Fora, Brazil.

Copyright

© 2021 Dr. Maurilio de Souza Cazarim, *et al.* This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 21 May 2021

Published: 26 May 2021

Keywords: *COVID-19; Patient Management; Palliative Treatment*

Abstract

The epidemiological reach of COVID-19, emerging pandemic disease, has aroused concern among stakeholders worldwide about patients' management. Understanding the factors that influence the management of the disease, which have not yet been fully elucidated, and understanding their associations in the planning actions to cope with disease. The aim was developed a systematic review

protocol for answer the question: What clinical variables are correlated to the clinical management of COVID-19 in primary, secondary and tertiary cares? This is a systematic review protocol which has followed the Cochrane guidelines for systematic review. This protocol showed a robust method to perform a systematic review about the identification of clinical variables that are associated to progression of COVID-19. The systematic review results can aid to improve the management of COVID-19 patients at the comprehensive care in Brazil.

Systematic Review Justification

The epidemiological reach of COVID-19, emerging pandemic disease, has aroused concern among stakeholders worldwide for two main reasons: clinical and epidemiological information on the disease is still poor in evidence; and the influence of the health sector in the world economy, which has had a strong impact to the point of causing one of the biggest economic recessions in history [1,2]. It is estimated that more than 170 countries will experience a negative growth in per capita income in the year of 2020, with a 5,3% decline of the Gross Domestic Product in Brazil, which may reach 9,0% [1].

Clinical variables have been doubting object as its relevance and targeting for clinical management of COVID19. Factors related to treatment, co-morbidities, alternative therapies, can build important indicators for the fittest COVID19 care. Additionally, it is important to measure for comprehensive care in the health system and, thus to have the conception for different levels of care. In Brazil, these levels can be resumed in primary (preventive and basic care), secondary (specialized care), and tertiary care (hospital and clinicians for complex procedures) in the Public Health System [2].

In this sense, understanding the factors that influence the management of the disease, which have not yet been fully elucidated, and understanding their associations in the planning actions to cope with disease, can represent a reduction in the health systems overload and a more assertive path for the recovery of the population's health. Fast actions and a proper management of patients infected with COVID-19 tend to soften economic impact, and this foster healthy feedback between the two sectors: health and economy [3].

Method

This protocol was registered at the base of PROSPERO - International Prospective Register of Systematic Reviews - for systematic review, number ID 256450 (<https://www.crd.york.ac.uk/prospero/>). Search strategy was performed to enhance methodological transparency and improve the reproducibility of the findings, following the PRISMA checklist [4]. Additionally, using the PICOS (Population/Intervention/Comparison/Outcomes/Study Design) acronym we elaborated questions of systematic reviews, to ensure the systematic search of scientific literature.

As COVID-19 is an emerging disease, works/articles began to be published in January 2020, so the comparator and outcomes will not be considered in the search strategy, as it is a little-known topic, described in the literature, which does not influence the specificity of systematic review, but rather improve the sensitivity [5].

Studies was retrieved from four electronic bibliographic databases: MEDLINE via PubMed, Cochrane Library by Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica database (EMBASE) via Elsevier and Latin American and Caribbean Health Sciences Literature (LILACS). In addition, secondary searches in other sources, such as Google Scholar will be also carried out. The reference section of the included studies will be hand-searched for additional relevant studies. The search strategy will comprise only key terms according to PICOS acronym. The studies will be selected through the following order: reading the title, abstract and full text. The data will be tabulated to list the main variables of the patients affected by COVID-19 and, thus, extract the characteristics of the study, sociodemographic characteristics and description of the intervention and control groups, if any, as well as the analyzed indicators. To access the quality of the studies, the validated Downs and Black (1998) instrument will be used, which comprises a checklist of 28 items [6]. It allows to verify the general quality of the study, the internal and external validity, bias, confusion, and the power of the analyzes. This measurement is performed by a generated score and can be applied to observational studies [6], which is interesting due to the need addressed in this systematic review and the openness given by the journals to this pandemic for publication on this topic. The selection will be carried out with the aid of the Rayyan platform for systematic reviews [7].

The structuring of this systematic review, based on the Cochrane guide for systematic review and meta-analysis, progressing in the stages of search, selection, data extraction, compilation and analysis and results [5].

Review Question

What clinical variables are correlated to the clinical management of COVID-19 in primary care, secondary care and tertiary care?

Need for Systematic Review

A literature search will be carried out with the need to establish a pattern of the main influential variables for the epidemiological scenario of COVID-19, also meet a demand from the Brazilian Public Health System and generate synthesis of evidence [2].

Objective of the Review

The objective is to understand and relate qualitatively the different variables that have been associated with the clinical management of the COVID-19 for creating of a patient management algorithm in the public health system in Brazil.

Search and Review's Strategy

The condition or the study domain will be defined for the management of COVID-19 developed in primary, secondary and tertiary health care. In addition, the treatments proposed, and respective clinical variables analyzed will be relevant to the domain of this themes [3].

The definition of research categories is based on two main categories for clinical trials (PICO) according to Higgins and Green (HIGGINS, GREEN, 2011) [7]. A summary of the Population (P), Interventions (I), Comparators (C) and Outcomes (O) considered, following the PICO acronym, is shown in table 1.

Table 1: Inclusion criteria

PICOS acronym	Inclusion criteria
P-Population	Patients diagnosed with COVID-19
I-Intervention	Treatments or therapies for COVID-19
C-Comparison	Not applicable
O-Outcome	Not applicable
S-Study design	Observational studies

The Boolean operators to be used are: intra-category “OR” for word combination and, inter-category “AND” for word combination, population and intervention. No search filters will be used. It is emphasized that the search groups should be divided according to PIC, and when combining the “OR” the terms/words should always be in parentheses because unlinking the “OR” in the search may find off-target results and provide a broad, inaccurate search. Descriptors and keywords were extracted from controlled vocabularies, Emtree thesaurus for the strategies assembled in EMBASE, Health Science Descriptors (DeCS) in Portuguese/Spanish/English for LILACS; MeSH (Medical Subject Headings) for PubMed, Cochrane e Scopus. The search was run on February 25th, 2021, in English, Portuguese and Spanish. The search strategies were adapted to each search base according to its peculiarities (Table 2).

Table 2: Concepts and search items

Primary care	
Databases	Search items
MEDLINE/CENTRAL	#1 (“COVID-19”[MeSH Terms]) OR (“COVID 19”[Text Word]) OR (“Disease, COVID-19 Virus”[Text Word]) OR (“Virus Disease, COVID-19”[-Text Word]) OR (“COVID-19 Virus Infection”[Text Word]) OR (“COVID 19 Virus Infection”[Text Word]) OR (“COVID-19 Virus Infections”[Text Word]) OR (“Virus Infection, COVID-19”[Text Word]) OR (“2019-nCoV Infection”[Text Word]) OR (“2019 nCoV Infection”[Text Word]) OR (“2019-nCoV Infections”[Text Word]) OR (“Coronavirus Disease-19”[-Text Word]) OR (“Coronavirus Disease 19”[Text Word]) OR (“2019 Novel Coronavirus Disease”[Text Word]) OR (“2019 Novel Coronavirus Infection”[Text Word]) OR (“2019-nCoV Disease”[Text Word]) OR (“2019 nCoV Disease”[Text Word]) OR (“2019-nCoV Diseases”[Text Word]) OR (“Disease, 2019-nCoV”[Text Word]) OR (“COVID19”[Text Word]) OR (“Coronavirus Disease 2019”[Text Word]) OR (“Disease 2019, Coronavirus”[Text Word]) OR (“SARS Coronavirus 2 Infection”[Text Word])

OR (“SARS-CoV-2 Infection”[Text Word])) OR (“Infection, SARS-CoV-2”[Text Word])) OR (“SARS CoV 2 Infection”[Text Word])) OR (“SARS-CoV-2 Infections”[Text Word])) OR (“COVID-19 Pandemic”[Text Word])) OR (“COVID 19 Pandemic”[Text Word])) OR (“COVID-19 Pandemics”[-Text Word])) OR (“Pandemic, COVID-19”[Text Word])) OR (“SARS-CoV-2”[MeSH Terms])) OR (“Coronavirus Disease 2019 Virus”[Text Word])) OR (“2019 Novel Coronavirus”[Text Word])) OR (“2019 Novel Coronavirus-es”[Text Word])) OR (“Coronavirus, 2019 Novel”[Text Word])) OR (“Novel Coronavirus, 2019”[Text Word])) OR (“Wuhan Seafood Market Pneumonia Virus”[Text Word])) OR (“SARS-CoV-2 Virus”[Text Word])) OR (“SARS CoV 2 Virus”[Text Word])) OR (“SARS-CoV-2 Viruses”[Text Word])) OR (“Virus, SARS-CoV-2”[Text Word])) OR (“2019-nCoV”[Text Word])) OR (“COVID-19 Virus”[Text Word])) OR (“COVID 19 Virus”[Text Word])) OR (“COVID-19 Viruses”[Text Word])) OR (“Virus, COVID-19”[Text Word])) OR (“Wuhan Coronavirus”[Text Word])) OR (“Coronavirus, Wuhan”[Text Word])) OR (“SARS Coronavirus 2”[Text Word])) OR (“Coronavirus 2, SARS”[Text Word])) OR (“Severe Acute Respiratory Syndrome Coronavirus 2”[Text Word]))

#2 (“Therapeutics”[MeSH Terms]) OR (“Therapeutic”[Text Word])) OR (“Therapy”[Text Word])) OR (“Therapies”[Text Word])) OR (“Treatment”[-Text Word])) OR (“Treatments”[Text Word])) OR (“Drug Therapy”[MeSH Terms])) OR (“Therapy, Drug”[Text Word])) OR (“Drug Therapies”[Text Word])) OR (“Therapies, Drug”[Text Word])) OR (“Chemotherapy”[Text Word])) OR (“Chemotherapies”[Text Word])) OR (“Pharmacotherapy”[-Text Word])) OR (“Pharmacotherapies”[Text Word])) OR (“Disease Management”[MeSH Terms])) OR (“Disease Managements”[Text Word])) OR (“Management, Disease”[Text Word])) OR (“Standard of Care”[MeSH Terms])) OR (“Care Standard”[Text Word])) OR (“Care Standards”[Text Word])) OR (“Standards of Care”[Text Word])) OR (“Palliative Care”[MeSH Terms])) OR (“Care, Palliative”[Text Word])) OR (“Palliative Treatment”[Text Word])) OR (“Palliative Treatments”[Text Word])) OR (“Treatment, Palliative”[Text Word])) OR (“Treatments, Palliative”[Text Word])) OR (“Therapy, Palliative”[Text Word])) OR (“Palliative Therapy”[Text Word])) OR (“Palliative Supportive Care”[Text Word])) OR (“Supportive Care, Palliative”[Text Word])) OR (“Primary Health Care”[MeSH Terms])) OR (“Care Primary Health”[Text Word])) OR (“Primary Care”[Text Word])) OR (“Care Primary”[Text Word])) OR (“Primary Healthcare”[Text Word])) OR (“Healthcare Primary”[Text Word])) OR (“Health Care Comprehensive”[Text Word])) OR (“Comprehensive Healthcare”[Text Word])) OR (“Healthcare Comprehensive”[Text Word])) OR (“First Line Care”[Text Word])) OR (“Health Care Primary”[Text Word])) OR (“Community Health Services”[MeSH Terms])) OR (“Health Services, Community”[Text Word])) OR (“Community Health Service”[Text Word])) OR (“Health Service Community”[Text Word])) OR (“Service Community Health”[Text Word])) OR (“Services Community Health”[Text Word])) OR (“Community Health Care”[Text Word])) OR

("Care Community Health"[Text Word])) OR ("Health Care Community"[Text Word])) OR ("Community Healthcare"[Text Word])) OR ("Healthcare Community"[Text Word])) OR ("Community Health Services"[Text Word])) OR ("Community Care Service"[Text Word])) OR ("Community Care Services"[Text Word])) OR ("Preventive Health Care"[Text Word])) OR ("Preventive Medicine"[MeSH Terms])) OR ("Preventative Medicine"[Text Word])) OR ("Medicine Preventative"[Text Word])) OR ("Preventive Medicine"[Text Word])) OR ("Preventive Care"[Text Word])) OR ("Care Preventive"[Text Word])) OR ("Care Preventative"[Text Word])) OR ("Outpatients"[MeSH Terms])

#3 ("disease progression"[MeSH Terms]) OR ("Disease Progression"[MeSH Terms])) OR ("Prognosis"[MeSH Terms])) OR ("Severity of Illness Index"[MeSH Terms])) OR ("Time-to-Treatment"[MeSH Terms]))

#4 ("mechanical ventilation"[Text Word]) OR ("fatal cases"[Text Word])) OR ("mortality"[MeSH Terms])) OR ("Severe Acute Respiratory Syndrome"[MeSH Terms])) OR ("critical care"[MeSH Terms])) OR ("severity"[Text Word])) OR ("intensive care"[Text Word])) OR ("Disease Exacerbation"[Text Word])) OR ("outpatient"[Text Word]) OR ("death"[Text Word])

#1 AND #2 AND #3 NOT #4

EMBASE

#1 ('covid 19'/exp OR 'covid 19' OR 'covid 19':ti,ab,kw OR '2019 novel coronavirus infection':ti,ab,kw OR covid19:ti,ab,kw OR 'coronavirus disease 2019':ti,ab,kw OR 'coronavirus disease-19':ti,ab,kw OR '2019-ncov disease':ti,ab,kw OR '2019 novel coronavirus disease':ti,ab,kw OR '2019-ncov infection':ti,ab,kw OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2' OR 'severe acute respiratory syndrome coronavirus 2':ti,ab,kw OR 'wuhan coronavirus':ti,ab,kw OR 'wuhan seafood market pneumonia virus':ti,ab,kw OR 'covid19 virus':ti,ab,kw OR 'covid-19 virus':ti,ab,kw OR 'coronavirus disease 2019 virus':ti,ab,kw OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR '2019 ncov':ti,ab,kw OR '2019 novel coronavirus':ti,ab,kw OR 'spike glycoprotein, covid-19 virus':ti,ab,kw OR 'covid-19 virus spike glycoprotein':ti,ab,kw OR '2019-ncov spike glycoprotein':ti,ab,kw)

#2 ('drug therapy'/exp OR 'drug therapy' OR 'chemotherapy':ti,ab,kw OR 'pharmacotherapy':ti,ab,kw OR 'disease management'/exp OR 'disease management' OR 'standard of care'/exp OR 'standard of care' OR 'palliative therapy'/exp OR 'palliative therapy' OR 'palliative supportive care':ti,ab,kw OR 'primary health care'/exp OR 'primary health care' OR 'health care comprehensive':ti,ab,kw OR 'community care'/exp OR 'community care' OR 'preventive medicine':ti,ab,kw)

#3 ('disease exacerbation'/exp OR 'disease exacerbation' OR 'disease exacerbation':ti,ab,kw OR 'prognosis'/exp OR 'prognosis' OR 'severity of illness index'/exp OR 'severity of illness index' OR 'time to treatment'/exp OR 'time to treatment' OR 'treatment outcome'/exp OR 'treatment outcome')

#4 ('mechanical ventilation':ti,ab,kw OR 'fatal cases':ti,ab,kw OR 'mortality':ti,ab,kw OR 'severe acute respiratory syndrome':ti,ab,kw OR 'critical care':ti,ab,kw OR 'severity':ti,ab,kw OR 'intensive care':ti,ab,kw OR 'disease exacerbation':ti,ab,kw OR 'outpatient':ti,ab,kw OR 'death':ti,ab,kw)

#1 AND #2 AND #3 NOT #4

LILACS

#1 ((Coronavirus AND Infections) OR (Infecções AND por AND Coronavirus) OR (Infecciones AND por AND Coronavirus) OR (Betacoronavirus) OR (2019-nCoV) OR (SARS-CoV-2) OR (Coronavirus AND da AND Síndrome AND Respiratória AND Aguda AND Grave AND 2) OR (Severe AND Acute AND Respiratory AND Syndrome AND Coronavirus AND 2) OR (SARS-CoV-2) OR (COVID-19) OR (2019-nCoV))

#2 ((Disease AND Progression) OR (Progressão AND da AND doença) OR (Progresión AND de AND la AND Enfermedad) OR (Survival AND analysis) OR (Análise AND de AND sobrevida) OR (Análisis AND de AND Supervivencia) OR (Prognosis) OR (Prognóstico) OR (Pronóstico) OR (Severity AND of AND Illness AND Index) OR (Índice AND de AND Gravidade AND de AND Doença) OR (Índice AND de AND Severidad AND de AND la AND Enfermedad) OR (Time-to-Treatment) OR (Tempo AND para AND o AND Tratamiento) OR (Tiempo AND de AND Tratamiento) OR (Avanço AND da AND Doença) OR (Disease AND Exacerbation) OR (Progresión AND de AND Enfermedad) OR (Tempo AND até AND o AND Tratamiento) OR (Análise AND de AND Sobrevivência) OR (Fatore\$ Prognóstico\$) OR (Prognostic Factor\$) OR (Factore\$ Pronostico\$) OR (Índice AND de AND Severidade AND da AND Doença) OR (Índice AND de AND Gravedad AND de AND la AND Enfermedad) OR (Delay\$ Treatment\$) OR (Tiempo AND para AND el AND Tratamiento) OR (Primary AND Health AND Care) OR (Atención AND Primaria AND de AND Salud) OR (Atenção AND Primária AND à AND Saúde) OR (Primary AND Care) OR (Atención AND Primaria) OR (Atenção AND Primária) OR (Atenção AND Básica) OR (Community AND Health AND Service\$) OR (Servicio\$ AND de AND Salud AND Comunitaria) OR (Serviço\$ AND de AND Saúde AND Comunitária) OR (Community AND Health AND Care) OR (Cuidado AND de AND Salud AND Comunitario) OR (Saúde AND Comunitária) OR (Preventive AND Medicine) OR (Medicina AND Preventiva) OR (Comprehensive AND Health AND Care) OR (Atención AND Integral AND de AND Salud) OR (Assistência AND Integral AND à AND Saúde))

#3 ((Drug AND Therapy) OR (Tratamiento AND Farmacológico) OR (Quimioterapia) OR (Palliative AND Care) OR (Cuidados AND Paliativos) OR (Patient AND Care AND Planning) OR (Planejamento AND de AND Assistência AND ao AND Paciente) OR (Planificación AND de AND Atención AND al AND Paciente) OR (Tratamiento AND Domiciliar) OR (Residential AND Treatment) OR (Tratamiento Domiciliario) OR (Therapeutics) OR

(Terapêutica) OR (Terapéutica) OR (Disease AND Management) OR (Gerenciamento AND Clínico) OR (Manejo AND de AND la AND Enfermedad) OR (Drug AND therapy) OR (Treatment AND Outcome) OR (Treatment AND Failure) OR (Homebound AND Person) OR (Pacientes AND Domiciliares) OR (Personas AND Imposibilitadas) OR (Conservative AND Treatment) OR (Tratamento AND Conservador) OR (Tratamiento AND Conservador) OR (Tratamento AND com AND Fármacos) OR (Pharmacotherapy) OR (Terapia AND con AND Fármacos) OR (Tratamiento AND com AND Medicamentos) OR (Terapia AND con AND Medicamentos) OR (Tratamiento AND Paliativo) OR (Palliative AND Therapy) OR (Atención AND Paliativa) OR (Residential AND Treatment) OR (Procedimiento AND de AND Tratamiento) OR (Ações AND Terapêuticas) OR (Medida AND Terapêutica) OR (Acción AND Terapéutica) OR (Procedimiento AND Terapéutico) OR (Pessoa AND Confinada AND em AND Domicílio) OR (House-Bound AND Person) OR (Monitoramento AND Conservador) OR (Conservative AND Management) OR (Manejo AND Conservador))

#4 ((mechanical AND ventilation) OR (fatal AND cases) OR (mortality) OR (Severe AND Acute AND Respiratory AND Syndrome) OR (critical AND care) OR (severity) OR (intensive AND care) OR (Disease AND Exacerbation) OR (outpatient) OR (death))

#1 AND #2 AND #3 NOT #4

Secondary care

Databases

Search items

MEDLINE/CENTRAL

#1 (“covid 19”[MeSH Terms] OR “covid 19”[Text Word] OR “disease covid 19 virus”[Text Word] OR “virus disease covid 19”[Text Word] OR “covid 19 virus infection”[Text Word] OR “covid 19 virus infection”[Text Word] OR “COVID-19 Virus Infections”[Text Word] OR “virus infection covid 19”[Text Word] OR “2019 ncov infection”[Text Word] OR “2019 ncov infection”[Text Word] OR “2019-nCoV Infections”[Text Word] OR “coronavirus disease 19”[Text Word] OR “coronavirus disease 19”[Text Word] OR “2019 Novel Coronavirus Disease”[Text Word] OR “2019 Novel Coronavirus Infection”[Text Word] OR “2019 ncov disease”[Text Word] OR “2019 ncov disease”[Text Word] OR “2019-nCoV Diseases”[Text Word] OR “disease 2019 ncov”[Text Word] OR “COVID19”[Text Word] OR “Coronavirus Disease 2019”[Text Word] OR “disease 2019 coronavirus”[Text Word] OR “SARS Coronavirus 2 Infection”[Text Word] OR “sars cov 2 infection”[Text Word] OR “infection sars cov 2”[Text Word] OR “sars cov 2 infection”[Text Word] OR “SARS-CoV-2 Infections”[Text Word] OR “covid 19 pandemic”[Text Word] OR “covid 19 pandemic”[Text Word] OR “COVID-19 Pandemics”[Text Word] OR “pandemic covid 19”[Text Word] OR “SARS-CoV-2”[MeSH Terms] OR “Coronavirus Disease 2019 Virus”[Text Word] OR “2019 Novel Coronavirus”[Text Word] OR “2019 Novel Coronaviruses”[Text Word] OR “coronavirus 2019 novel”[Text Word] OR “novel coronavirus 2019”[Text Word] OR

“Wuhan Seafood Market Pneumonia Virus”[Text Word] OR “sars cov 2 virus”[Text Word] OR “sars cov 2 virus”[Text Word] OR “SARS-CoV-2 Viruses”[Text Word] OR “virus sars cov 2”[Text Word] OR “2019-nCoV”[Text Word] OR “covid 19 virus”[Text Word] OR “covid 19 virus”[Text Word] OR “COVID-19 Viruses”[Text Word] OR “virus covid 19”[Text Word] OR “Wuhan Coronavirus”[Text Word] OR “coronavirus wuhan”[Text Word] OR “SARS Coronavirus 2”[Text Word] OR “coronavirus 2 sars”[Text Word] OR “Severe Acute Respiratory Syndrome Coronavirus 2”[Text Word] #2 (“Secondary Care”[MeSH Terms]) OR (“Care, Secondary”[Text Word])) OR (“Secondary Cares”[Text Word])) OR (‘secondary health care’[Text Word]) OR (‘secondary healthcare’[Text Word]) OR (‘secondary care center’[Text Word]) OR (‘secondary health-care facilities’[Text Word])

#1 AND #2

EMBASE

#1 (‘covid 19’/exp OR ‘covid 19’ OR ‘covid 19’:ti,ab,kw OR ‘2019 novel coronavirus infection’:ti,ab,kw OR ‘coronavirus disease 2019’:ti,ab,kw OR ‘coronavirus disease-19’:ti,ab,kw OR ‘2019-ncov disease’:ti,ab,kw OR ‘2019 novel coronavirus disease’:ti,ab,kw OR ‘2019-ncov infection’:ti,ab,kw OR ‘severe acute respiratory syndrome coronavirus 2’/exp OR ‘severe acute respiratory syndrome coronavirus 2’ OR ‘severe acute respiratory syndrome coronavirus 2’:ti,ab,kw OR ‘wuhan coronavirus’:ti,ab,kw OR ‘wuhan seafood market pneumonia virus’:ti,ab,kw OR ‘covid19 virus’:ti,ab,kw OR ‘covid-19 virus’:ti,ab,kw OR ‘coronavirus disease 2019 virus’:ti,ab,kw OR ‘sars cov 2’:ti,ab,kw OR sars2:ti,ab,kw OR ‘2019 ncov’:ti,ab,kw OR ‘2019 novel coronavirus’:ti,ab,kw OR ‘spike glycoprotein, covid-19 virus’:ti,ab,kw OR ‘covid-19 virus spike glycoprotein’:ti,ab,kw OR ‘2019-ncov spike glycoprotein’:ti,ab,kw)

#2 (‘drug therapy’/exp OR ‘drug therapy’ OR ‘chemotherapy’:ti,ab,kw OR ‘pharmacotherapy’:ti,ab,kw OR ‘disease management’/exp OR ‘disease management’ OR ‘standard of care’/exp OR ‘standard of care’ OR ‘palliative therapy’/exp OR ‘palliative therapy’ OR ‘palliative supportive care’:ti,ab,kw)

#3 (‘secondary care’/exp OR ‘secondary care’ OR ‘care, secondary’:ti,ab,kw OR ‘secondary cares’:ti,ab,kw OR ‘secondary health care’:ti,ab,kw OR ‘secondary healthcare’:ti,ab,kw OR ‘secondary care center’:ti,ab,kw OR ‘secondary health-care facilities’:ti,ab,kw)

#1 AND #2 AND #3

LILACS

#1 (Coronavirus AND Infections) OR (Infecções AND por AND Coronavirus) OR (Infecciones AND por AND Coronavirus) OR (Betacoronavirus) OR (2019-nCoV) OR (SARS-CoV-2) OR (Coronavírus AND da AND Síndrome AND Respiratória AND Aguda AND Grave AND 2) OR (Severe AND Acute AND Respiratory AND Syndrome AND Coronavirus AND 2) OR (SARS-CoV-2) OR (COVID-19) OR (2019-nCoV)) #2 ((Drug AND

Therapy) OR (Tratamento AND Farmacológico) OR (Quimioterapia) OR (disease AND management) OR (Gerenciamento AND Clínico) OR (Manejo AND de AND la AND Enfermedad) OR (disease AND exacerbation) OR (Progressão AND da AND Doença) OR (Progresión AND de AND la AND Enfermedad) OR (prognosis) OR (Prognóstico) OR (Pronóstico) OR (severe AND acute AND respiratory AND syndrome) OR (Síndrome AND Respiratória AND Aguda AND Grave) OR (Síndrome AND Respiratorio AND Agudo AND Grave))

#3 ((Outpatient AND Clinics AND Hospital) OR (Ambulatório AND Hospitalar) OR (Servicio AND Ambulatorio AND en AND Hospital) OR (Secondary AND Care) OR (Atención AND Secundaria AND de AND Salud) OR (Atenção AND Secundária AND à AND Saúde) OR (Secondary AND Health AND Care) OR (Cuidado AND de AND la AND Salud AND secundaria) OR (Cuidado\$ AND de AND saúde AND secundário\$) OR (Pulmonary Medicine) OR (Pneumologia) OR (Neumología))

#1 AND #2 AND #3

Tertiary care

Databases

Search items

MEDLINE/CENTRAL

#1 (“covid 19”[MeSH Terms] OR “2019 novel coronavirus infection”[Text Word] OR “covid19”[Text Word] OR “coronavirus disease 2019”[Text Word] OR “coronavirus disease-19”[Text Word] OR “2019-ncov disease”[Text Word] OR “2019 novel coronavirus disease”[Text Word] OR “2019-ncov infection”[-Text Word] OR “wuhan coronavirus”[Text Word] OR “wuhan seafood market pneumonia virus”[Text Word] OR “covid19 virus”[Text Word] OR “covid-19 virus”[Text Word] OR “coronavirus disease 2019 virus”[Text Word] OR “sars cov 2”[Text Word] OR “sars2”[Text Word] OR “2019 ncov”[Text Word] OR “2019 novel coronavirus”[Text Word])

#2 (“clinical characteristics”[Text Word] OR “severity of illness index”[Text Word] OR “severe acute respiratory syndrome”[Text Word] OR “mechanical ventilation”[Text Word] OR “severity”[Text Word] OR “intensive care”[Text Word])

#3 (“inpatients”[Text Word] OR “hospitals”[MeSH Terms] OR “inpatient”[-Text Word] OR “hospital”[Text Word])

#4 (“primary health care”[MeSH Terms] OR “preventive medicine”[MeSH Terms] OR “secondary health care” OR “mild”[Text Word] OR “milder”[Text Word] OR “primary care”[Text Word] OR “biomarkers”[Text Word] OR “protocol”[Text Word] OR “community healthcare”[Text Word] OR “health-care community”[Text Word] OR “community health services”[Text Word] OR “preventive medicine”[Text Word] OR “medicine preventive”[Text Word] OR “preventive care”[Text Word] OR “care preventive”[Text Word] OR “preventative medicine”[Text Word] OR “preventative care”[Text Word] OR “care

preventative"[Text Word] OR "health care comprehensive"[Text Word] OR "comprehensive healthcare"[Text Word] OR "healthcare comprehensive"[Text Word] OR "first line care"[Text Word] OR "health care primary"[Text Word] OR "community care service"[Text Word] OR "community care services"[Text Word] OR "preventive health care"[Text Word] OR "secondary health care"[-Text Word] OR "secondary healthcare"[Text Word] OR "care secondary"[-Text Word] OR "secondary care center"[Text Word] OR "mask"[Text Word] OR "genomic"[Text Word] OR "placental"[Text Word] OR "surgery"[Text Word] OR "systematic review"[Text Word] OR "lockdown"[Text Word] OR "swabs"[Text Word] OR "validation"[Text Word] OR "predict"[Text Word] OR "artificial intelligence"[Text Word] OR "machine learning"[Text Word])

#1 AND #2 AND #3 NOT #4

EMBASE

#1 ('covid 19'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'covid 19':ti,ab,kw OR '2019 novel coronavirus infection':ti,ab,kw OR 'covid19':ti,ab,kw OR 'coronavirus disease 2019':ti,ab,kw OR 'coronavirus disease-19':ti,ab,kw OR '2019-ncov disease':ti,ab,kw OR '2019 novel coronavirus disease':ti,ab,kw OR '2019-ncov infection':ti,ab,kw OR 'wuhan coronavirus':ti,ab,kw OR 'wuhan seafood market pneumonia virus':ti,ab,kw OR 'covid19 virus':ti,ab,kw OR 'covid-19 virus':ti,ab,kw OR 'coronavirus disease 2019 virus':ti,ab,kw OR 'sars cov 2':ti,ab,kw OR 'sars2':ti,ab,kw OR '2019 ncov':ti,ab,kw OR '2019 novel coronavirus':ti,ab,kw)

#2 ('clinical characteristics':ti,ab,kw OR 'severity of illness index':ti,ab,kw OR 'severe acute respiratory syndrome':ti,ab,kw OR 'mechanical ventilation':ti,ab,kw OR 'severity':ti,ab,kw OR 'intensive care':ti,ab,kw)

#3 ('inpatients':ti,ab,kw OR 'hospitals'/exp OR 'terciary care':ti,ab,kw OR 'inpatient':ti,ab,kw OR 'hospital':ti,ab,kw)

#4 ('primary health care'/exp OR 'community care'/exp OR 'preventive medicine'/exp OR 'secondary health care'/exp OR 'mild':ti,ab,kw OR 'milder':ti,ab,kw OR 'primary care':ti,ab,kw OR 'biomarkers':ti,ab,kw OR 'protocol':ti,ab,kw OR 'community healthcare':ti,ab,kw OR 'healthcare community':ti,ab,kw OR 'community health services':ti,ab,kw OR 'preventive medicine':ti,ab,kw OR 'medicine preventive':ti,ab,kw OR 'preventive care':ti,ab,kw OR 'care preventive':ti,ab,kw OR 'preventative medicine':ti,ab,kw OR 'preventative care':ti,ab,kw OR 'care preventative':ti,ab,kw OR 'health care comprehensive':ti,ab,kw OR 'comprehensive healthcare':ti,ab,kw OR 'healthcare comprehensive':ti,ab,kw OR 'first line care':ti,ab,kw OR 'health care primary':ti,ab,kw OR 'community care service':ti,ab,kw OR 'community care services':ti,ab,kw OR 'preventive health care':ti,ab,kw OR 'secondary health care':ti,ab,kw OR 'secondary healthcare':ti,ab,kw OR 'care secondary':ti,ab,kw OR 'secondary care center':ti,ab,kw OR 'mask':ti,ab,kw OR 'genomic':ti,ab,kw OR 'placental':ti,ab,kw OR 'surgery':ti,ab,kw OR 'lockdown':ti,ab,kw OR 'swabs':ti,ab,kw OR 'validation':ti,ab,kw OR 'predict':ti,ab,kw OR 'artificial

intelligence':ti,ab,kw OR 'machine learning':ti,ab,kw)

#1 AND #2 AND #3 NOT #4

LILACS

#1 (Coronavirus AND Infections) OR (Infecções AND por AND Corona-
virus) OR (Infecciones AND por AND Coronavirus) OR (Betacoronavirus)
OR (2019-nCoV) OR (SARS-CoV-2) OR (Coronavírus AND da AND Sín-
drome AND Respiratória AND Aguda AND Grave AND 2) OR (Severe
AND Acute AND Respiratory AND Syndrome AND Coronavirus AND 2)
OR (SARS-CoV-2) OR (COVID-19) OR (2019-nCoV)

#2 (Drug AND Therapy) OR (Tratamento AND Farmacológico) OR (Quim-
ioterapia) OR (disease AND management) OR (Gerenciamento AND Clíni-
co) OR (Manejo AND de AND la AND Enfermedad) OR (disease AND ex-
acerbation) OR (Progressão AND da AND Doença) OR (Progresión AND de
AND la AND Enfermedad) OR (prognosis) OR (Prognóstico) OR (Pronósti-
co) OR (severity AND of AND illness AND index) OR (Índice AND de
AND Gravidade AND de AND Doença) OR (Índice AND de AND Seve-
ridad AND de AND la AND Enfermedad) OR (severe AND acute AND
respiratory AND syndrome) OR (Síndrome AND Respiratória AND Aguda
AND Grave) OR (Síndrome AND Respiratorio AND Agudo AND Grave)

#3 (inpatients) OR (Pacientes AND Internados) OR (Pacientes Internos) OR
(Outpatient AND Clinics AND Hospital) OR (Ambulatório AND Hospita-
lar) OR (Servicio AND Ambulatorio AND en AND Hospital) OR (Hospital
AND Care) OR (Assistência AND Hospitalar) OR (Atención AND Hospi-
talaria)

#4 (Primary AND Health AND Care) OR (Atenção AND Primária AND à
AND Saúde) OR (Atención AND Primaria AND de AND Salud) OR (Com-
munity AND Health AND Services) OR (Serviços AND de AND Saúde
AND Comunitária) OR (Servicios AND de AND Salud AND Comunitaria)
OR (Preventive AND Medicine) OR (Medicina AND Preventiva)

#1 AND #2 AND #3 NOT #4

Subtitle: MEDLINE, Medical Literature Analysis and Retrieval System Online; CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica Database; LILACS, Latin American and Caribbean Health Sciences Literature. For The LILACS, it must be used the DeCS and, of these descriptions/keywords, the translation into the Portuguese and Spanish from the dictionary should be used when searching for words in the various fields.

The selected articles after reading the title and abstract will be fully analyzed to be included those studies that answer the question of the systematic review and that meet with the inclusion, exclusion, and eligibility criteria. Conflicts of article selection will be mutually resolved, when it is not agreed by the authors, a third researcher will have the decision-making power. In addition, original articles will be considered and limited to the languages english, spanish and portuguese. It should be noted that clinical trials will be analyzed in a separate group from other studies, and divided between randomized and non-randomized. Additionally,

meta-analyses and systematic reviews will not be included in the results of the review, since this would require another course for the systematic review. The following inclusion and exclusion criteria are listed.

Inclusion Criterias

Studies with patients diagnosed with COVID-19 on pharmacological or non-pharmacological treatment for COVID-19 with the clinical management of COVID-19 at primary, secondary and tertiary levels of health care.

Exclusion Criterias

Studies that did not consider the treatment of patients diagnosed with COVID-19; studies that analyze variables that are not reproducible for interventions regarding the clinical management of COVID-19; studies that do not point out variables correlated to the care of the patient with COVID-19; the variables described in the clinical management do not have clarity regarding their correlation with the disease; studies of narrative or integrative reviews, dissertations or theses, editorials, news, comments, letters to the editor, abstracts published in proceedings of scientific journals or congresses, and guidelines; studies that do not contemplate the PICO strategy.

Condition or Domain Covered in the Study

It's important to know that this review was divided into three systematic reviews. It is important to know about clinical variables that have influences on patients' final outcomes. They must be summarized differently at primary, secondary and tertiary cares. In this sense, the studies must bring results that show the association among clinical variables and outcomes for COVID-19 patients.

Measures of Effect

The effect will be measured by Relative Risks for experimental studies and odds ratio for observational studies reasoned in extracting those significant variables from selected studies in this review.

The eligibility of the studies found will be analyzed for the studies included in the review and will follow the criteria according the previously prepared checklist:

1. Evaluator's name;
2. Study ID:
 - Author, title and reference.
3. Eligibility requirements:
 - Verification of all items described in the inclusion criterion;
 - Biases that compromise the study due to potential conflicts of interest;

- Availability of data to be included in the systematic review.

4. Eligibility confirmation:

- Considering the course of the study, the intervention, the people involved, the study has potential to be included (The study's course is stated and consistent with the methods);
- Participants consistent with the purpose of the study; Interventions considered are consistent with the study's proposal;
- The evaluated results are consistent with the study's proposal)? (Yes or No)

The data synthesis and tabulation will occur in such a way that the quantitative and qualitative data have been extracted from the studies included in the review using the data form developed by the reviewers (excel table template). After the end, the collaborators will assist in the discussion and interpretation of the analyzed data for the set of variables.

Risk of Bias Assessment (Quality Assessment):

Initially, the bias assessment will be performed using the Cochrane *guideline* of bias risk classification [5]. The risk of bias assessment will be evaluated for clinical trials and observational studies in order to assess the quality of the study, Downs and Black instrument will be used, that makes up a 28-item checklist (allows to check the overall quality of the study, the internal and external validity, biases, confounding and power of the analyses).

Stage of Data Extraction

- Identification of clinical variables associated with the clinical course and management of COVID-19;
- Assemble the Excel spreadsheet with the categories of variables selected added in columns;
- Start the data extraction as:

o Fundamental variables:

1. Year
2. Reference
3. Country
4. Author
5. Planned sample number

o Details of the methods:

1. Type of study

2. Study design (how many groups; mode of data analysis)
 3. Follow-up time
 4. Randomization (“adequate”, “inadequate” or “not reported” by the study)
 5. Confidential allocation (reported or unreported)
 6. Blinding scheme:
 - Investigators - “yes”, “no” or “not reported”
 - Participants - “yes”, “no” or “not reported”
 - Outcome evaluators - “yes”, “no” or “not reported”
- o Participants:
1. Number of patients randomized by treatment mode or divided between comparison groups (exposed and unexposed)
 2. Number of follow-up losses per group
- o When clinical trials: clinical protocol
- Study phase
 - Type of screening (inclusion criteria and sample planning)
 - Assessment of safety and/or effectiveness
 - Gold standard comparator (placebo or standard treatment? Which one?)
 - Others.
- o Health care level:
1. Primary or preventive
 2. Emergency
 3. Hospital: Outpatient
 4. Hospital: Hospitalization
 5. Hospital: ICU admission COVID-19
- o Treatment
- Self-isolation only
 - Basic medication + Self-isolation
 - Basic medication + exams + hospitalization
 - Oxygen therapy

- Intubation + sedation
- Renal Therapy
- High technological density procedures
- Outcomes
 - Definition of each outcome investigated given the clinical condition of the study population;
 - Unit of measure (if applicable) used as the gold standard (yes or no)
 - Define death or survival
 - Define disability or sequela criteria
 - Perfect health, as before the disease
 - For scales:
 - report the upper and lower limits;
 - report how high or low the score is and whether there has been clinical improvement
 - Results
 - For each outcome, report categorical and/or continuous and/or discrete variables.
 - Calculate the rate of remission or recovery (control of clinical condition)
- 1. Sociodemographic descriptive data:
 - Average age
 - Percentage of sex
 - Average income
 - Education
 - Ethnicity
 - Previous disease history
 - Comorbidities
 - History of health events associated with CNCD
- 2. Clinical parameters of clinical interest:
 - Staging the population's risk
 - Obesity
 - Smoker

- Alcoholic
- Types of pre-existing diseases

Others

Note: Data referring to baseline characteristics of patients between studies summarize clinical heterogeneity. The difference between the comparative base of the study population can influence the extrapolation of the results. Thus, the protocol of this review provides for investigating which subgroups at each level of health care, including confounding factors that may contribute to the inconsistency of the findings: analyzing the difference in groups between the variables of age, sex, comorbidities, for example.

Analysis of the Results

Before the moment of consensus between the two researchers, the agreement between them will be analyzed by the Kappa coefficient, with a value above 0.80 being acceptable, otherwise, there will be a need to restructure a new search strategy. The Mann-Whitney test will be performed to test the difference between the quality scores of the studies with favorable and unfavorable clinical results. Other statistics will be used according to the behavior of the variables to be analyzed.

- Analysis of subgroups or subsets: The extraction of data for each level of care will be planned together, which will allow the listing of important subgroups or sets to be analyzed.

Main Outcome

Correlation degree of the clinical variable to the progression or remission of COVID-19.

- Primary outcomes

Correlation degree of the clinical variable to the progression or remission of COVID-19.

- Secondary outcomes

Patients' features or co-variables associated with the progression or remission of COVID-19.

Bibliography

1. Lamucci, S. & Globo Valor, O. (2020). *FMI projeta retração de 5,3% para economia brasileira em 2020*.
2. Opas - Organização Pan-Americana de Saúde (2020). *Folha informativa - COVID-19 (doença causada pelo novo coronavírus)*. Brasília: Opas, 2020.
3. Brasil (2020). *Ministério da Economia. Medidas do grupo de monitoramento dos impactos da COVID-19 pandemia*.

4. Shamseer L., Moher D., Clarke M., Ghersi D., Liberati A., Petticrew M., *et al.* (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*, 349, g7647.
5. Higgins, J. P. T. & Green, S. (2008). *Cochrane Reviewers' Handbook, Version 5.1: Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration, 2008.
6. Downs, S. H. & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. *J Epidemiol Community Health*, 8(52), 377-384.
7. Ouzzani, M., Hammady, H., Fedorowicz, Z., *et al.* (2016). Rayyan - a web and mobile app for systematic reviews. *Systematic Reviews*, 5(210).