Panel of COVID-19 phenotypes: systematic review protocol

Luciana Carvalho Silveira (lucianacsilveira@yahoo.com.br)
Federal University of Goias: Universidade Federal de Goias https://orcid.org/0000-0002-5764-2843
Yanca Carollynne Souza Moraes
Pontifical Catholic University of Goiás: Pontificia Universidade Catolica de Goias
Rodrigo da Silva Santos
Federal University of Goias: Universidade Federal de Goias
Angela Adamski da Silva Reis
Federal University of Goias: Universidade Federal de Goias

Research Article

Keywords: sars cov2, covid 19, risk factor, symptoms, phenotype, prevalence, incidence

Posted Date: July 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-713005/v1

Panel of COVID-19 phenotypes: systematic review protocol

Luciana Carvalho Silveira[1], Yanca Carollynne Souza Moraes[2], Rodrigo da Silva Santos[1], Angela Adamski da Silva Reis[1]

[1]Luciana Carvalho Silveira. Laboratory of Molecular Pathology, Department of Biochemistry and Molecular Biology, Institute of Biological Sciences, Federal University of Goiás (UFG), lucianacsilveira@yahoo.com.br ORCID: 0000-0002-5764-2843

[2]Yanca Carollynne Souza Moraes. School of Social Sciences and Health, Pontifical Catholic University of Goiás, yanca7moraes@gmail.com ORCID: 0000-0003-1027-5932

[1]Rodrigo da Silva Santos. Laboratory of Molecular Pathology, Department of Biochemistry and Molecular Biology, Institute of Biological Sciences, Federal University of Goiás (UFG) rdssantos@ufg.br ORCID: 0000-0002-9480-4362

[1]Angela Adamski da Silva Reis. Laboratory of Molecular Pathology, Department of Biochemistry and Molecular Biology, Institute of Biological Sciences, Federal University of Goiás (UFG) angela@ufg.br ORCID: 0000-0002-8281-7334

Corresponding author: Luciana Carvalho Silveira, lucianacsilveira@yahoo.com.br Esperança Avenue, Laboratory of Molecular Pathology, Department of Biochemistry and Molecular Biology, Institute of Biological Sciences, Federal University of Goiás (UFG), Goiânia, GO, Brazil.

Abstract

Background: The pandemic caused by the SARS-CoV-2 virus, called coronavirus disease 2019 (COVID-19), had an unexpected impact on much of the world, especially Brazil. People diagnosed with the virus manifest different levels of respiratory symptoms, ranging from mild to severe, and may need mechanical ventilation support. The interaction different factors lead to the development of a spectrum of time-related diseases in different phenotypes.

Methods: This review will consider observational studies published from December 2019 to July 2021, without language restrictions. Studies involving human subjects, adult participants (18 years and older), with subjects who have received a COVID-19 diagnosis using the reverse transcriptase polymerase chain reaction (RT-PCR) test as a reference for the detection of the SARS- CoV-2 virus, according to World Health Organization (WHO) guidance. The databases to be searched will include PubMed/MEDLINE, EMBASE, and CINAHL. The grey literature will also be searched for published research and unpublished studies, using Google Scholar. wo reviewers will independently screen all citations, full-text articles and abstract data. Potential conflicts will be resolved through discussion. Findings will be reported using a narrative synthesis of the results will be carried out around the prevalence, severity of the disease, mortality and risk among the different phenotypes of COVID-19. The I^2 statistic will be used to examine the heterogeneity between the studies, if possible, the meta-analysis will be conducted using the RStudio® statistical software package, and the data will be displayed using forest graphics.

Discussion: This review will disclose a panel of the different manifestations of the disease COVID-19, and to identify the real risk factor for the most serious phenotypes.

Systematic review registration: This protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020211439)

Keywords: “sars cov2”; “covid 19”; “risk factor”; “symptoms”; “phenotype”; "prevalence" and "incidence".

Background

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 virus, called coronavirus disease 2019 (COVID-19), had an unexpected impact on much of the world, especially Brazil. People diagnosed with the virus manifest different levels of respiratory symptoms, ranging from mild to severe, and may need mechanical ventilation support (1). The different patterns of manifestation of COVID-19 observed and detailed in different studies, depends on the interaction between three factors: (a) the severity of the infection, the host's response, the physiological reserve and the comorbidities; (b) the patient's ventilatory response to hypoxemia; (c) the time elapsed between the onset of the disease and monitoring and observation by a health team (2).

The interaction between these factors leads to the development of a spectrum of time-related diseases in different phenotypes. Like Richard Dawkins, he extrapolated the concept of Extended Phenotype, not merely being a product of the genotype, but influenced to varying degrees by the environment and the possible interaction between the two (3). It is possible through good assessment tools to identify these phenotypes (4). The tool of importance and prominence in the diagnosis of COVID-19, is the Computed Tomography (CT) of the chest, however, it cannot alone confirm it or exclude it. When the reverse-transcriptase polymerase chain reaction (RT-PCR) is used as a reference for the detection of the virus, chest CT has high sensitivity (97%), but low specificity (25%), given the overlap of findings with pulmonary infections of different etiologies. Above all, multiple articles were published reporting the tomographic findings of this condition, even in patients with negative RT-PCR results, emphasizing the role of CT in the current clinical setting (5).

Tomographic findings, pathophysiological mechanisms, and possible mechanisms of disease progression are being divided into stages by different authors. In the initial phase characterized by SARS-CoV-2 infection, flu-like symptoms can develop, mainly due to the viral infection itself (6). CT scans can already be seen, pulmonary opacities in single, double or scattered ground-glass, nodules located in the central lobe surrounded by irregular patches of glass opacities, irregular consolidation and air bronchogram signal (7). The second stage of pulmonary inflammation and coagulopathy, which can develop consecutively, demonstrate on CT the massive accumulation of cell-rich exudates in the alveolar cavity, vascular expansion and exudation in the interstitium with light consolidations (8). The third stage of the disease is characterized by pulmonary

fibrosis arising from the fibrous exudation of the alveolar cavity with multiple irregular consolidations (7).

In addition, increased levels of inflammatory biomarkers such as C-reactive protein (CRP), ferritin, Interleukin-6 (IL-6), Interleukin-1 (IL-1) and D-dimer are associated with the development of acute respiratory distress syndrome (ARDS) and a course unfavorable clinical outcome (8). The stages of the disease and its broad clinical spectrum, allows the description of specific individual phenotypes, considering hypoxemia as the severity marker (9). Rello et all describes 3 phenotypes based on respiratory symptoms, CT, hypoxemia, respiratory rate (RF), peripheral oxygen saturation (SpO_2) by pulse oximetry, in addition to interleukin-6 (IL-6) to differentiate phenotype 2 from 3 , due to the high inflammatory pattern of viral disease of completely unexpected evolution (9).

With respect to patients requiring mechanical ventilation, three respiratory phenotypes are named and explained by different authors (2,7,9). Indicators such as lung weight, CT, ventilation / perfusion ratio (V / Q), pulmonary compliance and elastance, fraction of cardiac output, right-to-left shunt and alveolar recruitment capacity are discussed among the authors, but with inconclusive outcomes. It is believed that the underlying pathophysiological mechanisms differ significantly between the phenotypes, thus requiring careful evaluation, different treatments and different results. The interaction between these factors leads to the development of a spectrum of time-related diseases in different phenotypes. Phenotype is not merely a product of genotype, but is influenced to varying degrees by the environment, and the possible interactions between the two.

The *primary objective* of this systematic review is to address a gap, summarizing the evidence from observational studies, randomized and cluster-randomized clinical trials. Through good assessment tools and analysis of all indicators and biological markers to form a panel of phenotypes of COVID-19, each with its particularities, specific treatments and epidemiological data. In this review we will define what are the different phenotypes of presentation of the disease, the stages of the disease distributed over a wide clinical spectrum, described specifically by the clinical symptoms, tomographic findings, pathophysiological mechanisms, and possible mechanisms of disease progression, considering hypoxemia, levels of inflammatory biomarkers, as well as the risk factors that exist or not for the development of severe forms of the disease. Mortality rates in risk groups, as well as the prevalence of the disease and its manifestations in parts of the

population, as well as comparisons between severities in people in the same group, will also be objectives of the research.

Methods

Protocol and registration

This protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42020211439) (10) and is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (11,12) (see checklist in Additional file 1). Any amendments to this protocol will be documented and published alongside the results of the systematic review. An etiology and risk review are design to assess associations between various variables, epidemiological factors and the outcomes. Not able to determine causality; rather it is only able to infer correlations or relationships between variables. The exposure of interest refers to a particular risk factor or several factors associated with a disease, condition of interest in a population, group, cohort who have been exposed to them. The framework details five different stages in the process of conducting a good review: (1) identifying the research question, (2) identifying relevant studies, (3) selecting the studies, (4) charting the data and (5) reporting the results (13).

Stage 1: Defining the research questions

How have COVID-19 epidemiological studies considered the disease heterogeneity? The specific research questions that will be addressed are:

1- What are the different phenotypes of patients with COVID-19 worldwide?
2- What are the real risk populations that are in contact with the SARS-CoV-2 virus who have developed disease severity phenotypes?

Eligibility criteria

The PEO framework ('Population–Exposition–Outcome') was used to clearly define the concepts in the main review question.

Inclusion Criteria

Population

We will include studies involving human subjects, adult participants (18 years and older) of any ethnicity, in any country, without language restrictions published from December 2019 to July 2020 the type observational studies.

Exposition

Subjects who have received a COVID-19 diagnosis using the reverse transcriptase polymerase chain reaction (RT-PCR) test as a reference for the detection of the SARS-CoV-2 virus, according to World Health Organization (WHO) guidance.

Outcomes

The studies selected for this review will assess the different clinical manifestations of the study period, study population, characteristics of participants (symptoms, CT findings, blood tests, hypoxemia, treatment, hospitalization days) individual or group and outcomes in Table 1.

Table 1. Study Eligibility Criteria

PANEL OF DISEASE									
Reference (Location)	**Study period**	**Study population**	**Symptoms**	**CT findings**	**Blood tests**	**Hypoxemia**	**Treatment**	**Days in Hospital**	**Outcomes**

Details on the intervention administered and comparison, the duration of prognostic indicators, mortality, primary results, incidence, prevalence, morbid, will be the second stage of da analyses the articles.

Exclusion criteria

We will exclude studies including participants under the age of 18 or those diagnosed with end-stage chronic disease or in palliative care will be excluded.

Stage 2: Identifying relevant studies

The search strategy will be designed to identify published and unpublished studies. An initial limited search of PubMed/MEDLINE was conducted to identify articles on this topic, followed by an analysis of the text words contained in the titles and abstracts, and the index terms used to describe those articles.

The databases to be searched will include PubMed/MEDLINE, EMBASE, and CINAHL.

The grey literature will also be searched for published research and unpublished studies, using Google Scholar.

The search terms to be used will be as follows:

Step 1: "sars cov2" with Boolean OR for "covid 19" with Boolean AND for "prevalence", "incidence". Step 2: “sars cov2” with Boolean OR for “covid 19” with Boolean AND for “risk factor”, “symptoms” and “phenotype”. (Additional file 2).

Stage 3: Study selection process

All the citations from the selected databases, the grey literature and other sources will be identified linked and loaded into Mendeley bibliographic software (Elsevier, London, UK) and duplicates will be removed. The screening process will be in two steps. The first step will involve the first author (LCS) and a second reviewer each independently screening the title and abstract of all retrieved citations for eligibility based on the specified inclusion and exclusion criteria. This will then be reviewed by the rest of the research team and, on consensus, move to the next step where relevant citations will be included in the full-text review. The first author (LCS) and a second reviewer will independently review the full texts to assess eligibility using the specified criteria. The rest of the research team will again review this process until full consensus is attained. If disagreements arise between (LCS) and a second reviewer at both stages of the screening process, a third reviewer (RSS) will be brought in as a moderator and make the final decision. The studies that meet the inclusion criteria will be recovered in full and their details extracted. The full texts of the selected studies will be submitted to a critical evaluation process. The critical evaluation will be carried out by two independent reviewers (LCS and YCSM) using the standardized critical evaluation instruments from the Joanna Briggs Institute (JBI) - Critical Appraisal Tools for the specifically studies found (13,14).

Stage 4: Extracting and charting the data

A data extraction form will be designed and used to extract equivalent information from each study. Data extraction forms will be piloted initially on a small number of included studies. Subsequently, each of the included studies will be abstracted by two reviewers, independently, and potential conflicts will be resolved through discussion. A panel will be developed that addresses the research questions and the aim of the review.

For the epidemiological studies, will use the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (15).

The data extracted will be discussed by the research team then summarized and tabulated in themes that address the research questions. Data to be extracted will include, but not be limited to study design, country, study setting, population characteristics, sampling and recruitment of participants, data collection, exposure and outcome variables of interest, characteristics of study participants, identified environmental risk factors, confounders and important conclusions reached from the study.

Stage 5: Collating, summarizing and reporting the results

The study selection process will be epitomized in a flow chart adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (11). The data from each study (e.g. study characteristics, context, participants, outcomes, limitations) will be used to build evidence tables of an overall description of included studies. A qualitative synthesis to assess the methodological quality of the studies will be carried out and will proceed to the quantitative synthesis (meta-analysis).

For the application of the most appropriate meta-analytical model and obtaining the combined estimate, the I^2 test will be used to estimate the proportion of total variability in point estimates attributed to heterogeneity different from that due to chance. The data will be grouped according to the level of heterogeneity between the studies, using the following strategy:

• I^2 <25%, meta-analysis of fixed effects to estimate the common prevalence (CI95%), assuming that the variability between all or most of the study is due to chance;

• I^2 25-75%, meta-analysis of random effects to estimate mean prevalence (CI95%);

• I^2> 75%, very large heterogeneity for the summary estimate to be calculated.

RStudio® software was used to group the results of the included studies.

After this test, thematic analysis and visual representations including maps or diagrams will be made available. We will use our results to (1) determine the panel of phenotypes COVID-19 in the world (2) the comorbidities considered, lifestyle factors, to determine all the risk indicators existing or not for the development of severe forms of disease.

Discussion

This review will contribute to the literature by summarizing the evidence to report the different existing phenotypes for COVID-19, and the real risk factors for the disease, together with their incidence and prevalence. To correlate the results of our study with the findings of different studies, facilitating discussion about the problem and its possible solution. The divergences in the data published by researchers in relation to mortality rates in risk groups, as well as the prevalence of the disease and its manifestations in parts of the population will be considered. This review will disclose the true etiology of the progression of the severity of the disease, as well as comparisons between severities in people in the same group, will also be elucidated. It is hoped that it will be possible to assemble a panel of the different manifestations of the disease COVID-19, and to identify the real risk factor for the most serious phenotypes.

At a larger review level, we anticipate that some outcomes may not have been sufficiently studied, resulting in inconclusive review results. As part of our review, we will identify knowledge strengths and gaps related to this area of inquiry. The findings of this review will be shared through peer-reviewed publications in academic journals, conference presentations, and knowledge translation packages to inform community knowledge users and government decision-makers developing effective interventions to support of rehabilitation after COVID-19.

Additional file 1. PRISMA-P 2015 Checklist.

Additional file 2. Detailed search strategy from PubMed/MEDLINE.

Abbreviations

SARS-cov-2: severe acute respiratory syndrome coronavirus; COVID- 19: Coronavirus disease 2019; CT: Computed Tomography; RT-PCR: Reverse-Transcriptase Polymerase Chain Reaction; CRP: C-reactive protein; IL-6: Interleukin-6; IL-1: Interleukin 1; ARDS: acute respiratory distress syndrome; RF: respiratory rate; SpO_2: peripheral oxygen saturation; V/Q ventilation / perfusion ratio; PROSPERO: Prospective Register of Systematic Reviews; PRISMA-P Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta- Analyses extension for Scoping Reviews checklist; PEO: 'Population–Exposition–Outcomes' framework; WHO: World Health Organization; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology checklist; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Acknowledgements

Not applicable.

Authors' contributions

LCS developed the concept and RSS and AASR reviewed the idea. LCS designed the search strategy and prepared an initial draft under the guidance of RSS and AASR. YCSM edited the manuscript and will be the second reviewer. All authors (LCS, RSS and AASR) approved the final version of the manuscript.

Funding

Not applicable.

Availability of data and materials

All data generated or analyzed during this study will be included in the published review article and will be available upon request.

Ethics approval and consent to participate

Systematic review—not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) [Internet]. Vol. 46, Intensive Care Medicine. Springer Berlin Heidelberg; 2020. 854–887 p. Available from: https://doi.org/10.1007/s00134-020-06022-5
2. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med [Internet]. 2020;46(6):1099–102. Available from: https://doi.org/10.1007/s00134-020-06033-2
3. Richard Dawkins. The Extended Phenotype-The Gene as the Unit of Selection. Vol. 1, Oxford University Press. New York - United States of America; 1982.
4. Zhao HM, Xie YX, Wang C. Recommendations for respiratory rehabilitation in

adults with coronavirus disease 2019. Chin Med J (Engl). 2020;133(13):1595–602.

5. Chate RC, Kaiser E, Nunes U, Bastos R, Passos D, Borges G, et al. Apresentação tomográfica da infecção pulmonar na COVID-19 : experiência brasileira inicial. J Bras Pneumol 2020;46(2). 2020;46(2):2–5.

6. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-NCoV). Radiology. 2020;295(1):202–7.

7. Robba C, Battaglini D, Ball L, Patroniti N, Loconte M, Brunetti I, et al. Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. Vol. 279, Respiratory Physiology and Neurobiology. 2020. p. 103455.

8. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol [Internet]. 2020; Available from: http://dx.doi.org/10.1038/s41379-020-0603-3

9. Rello J, Storti E, Belliato M, Serrano R. Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers. Eur Respir J [Internet]. 2020;55(5):4–7. Available from: http://dx.doi.org/10.1183/13993003.01028-2020

10. Silveira LC, Santos R da S, Reis AA da S. COVID-19 phenotype panel: systematic review protocol. PROSPERO 2020 CRD42020211439 [Internet]. 2020;1–3. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=211439

11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ [Internet]. 2015;349(January):1–25. Available from: http://dx.doi.org/doi:10.1136/bmj.g7647

12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;(January):1–9.

13. Aromataris E MZ (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Joanna Briggs Inst Rev Man 2020; doi:10.46658/JBIMES-20-01

14. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K MP-F. Explanation of Analytical Cross Sectional

366 Studies Critical Appraisal. JBI Man Evid Synth 2020;1–5.
367 https://joannabriggs.org/critical_appraisal_tools
368 15. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP.
369 The Strengthening the Reporting of Observational Studies in Epidemiology
370 (STROBE) statement: Guidelines for reporting observational studies. PLoS Med.
371 2007;4(10):1623–7.
372 16. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M et al. Cochrane
373 handbook for systematic reviews of interventions. 2nd ed. Chichester: John
374 Wiley & Sons; 2019. Cochrane. 2020;
375

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additional2.Detailedsearchstrategy.pdf
- Additionalfile1.PRISMAP2015Checklist.pdf
- ProtocoloPROSPERO.pdf