Genetic variants and susceptibility to severe COVID-19: a scoping review protocol

Estephania Candelo, Juan David Gutiérrez-Medina, Andrés Gempeler, Lorena Diaz-Ordoñez, Harry Pachajoa

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Estephania Candelo[1] MD, MPhil; Juan David Gutiérrez-Medina[1] BSc; Andrés Gempeler[1] MD, MSc; Lorena Diaz-Ordoñez[2] BSc, MSc; Harry Pachajoa[1] MD, PhD

[1]Fundacion Valle del lili Cali CO
[2]Universidad Icesi Cali CO

Corresponding Author:
Estephania Candelo MD, MPhil
Fundacion Valle del lili
Cra. 98 # 18-49, Cali, Valle del Cauca
Cali
CO

Abstract

Background: Coronavirus disease 19 (COVID-19), the disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is already responsible for more than four and a half million deaths worldwide. With a unique pathophysiology related to respiratory failure due to interstitial pneumonia and acute respiratory distress syndrome, severe COVID-19 is qualitatively different from moderate disease. Since genetics play a crucial role in susceptibility to viral infection and propensity to develop harmful inflammatory conditions, genetic heterogeneity promotes the question of whether gene variants might influence COVID-19 outcomes. The identification of genetic variants associated with severe courses of COVID-19 is a promising option for the improvement of prognostic tools, contemplation of new therapeutic targets and the development of patient's clinical risk stratification.

Objective: We aim to perform a scoping review to assess the extent of the literature regarding the gene variants that could be associated with COVID-19 severity.

Methods: The proposed scoping review will be conducted in accordance with the methodology from the Joanna Briggs Institute's Scoping Review Network.12 The search strategy will focus on published studies without discriminating in date or language. A multiple-database search (MEDLINE, LILACS, The Cochrane Library, Science Direct, Google Scholar and OpenGrey) will be done performing the following strategy: ((("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh]) AND ("Polymorphism, Genetic"[Mesh] OR "Mutation"[Mesh] OR "Antibody Diversity"[Mesh] OR "Antigenic Variation"[Mesh]) AND ("Severity of Illness Index"[Mesh] OR "Death"[Mesh] OR "Critical Care"[Mesh] OR "Critical Illness"[Mesh] OR (severity))). This scoping review will consider observational studies and genome-wide association studies (GWAS) without discriminating in date or language. Additionally, systematic reviews that meet the inclusion criteria will also be considered. Data will be extracted from papers included in the scoping review by two independent reviewers using an already existent data extraction tool.

Results: The conducted search was performed on February 16th in MEDLINE, LILACS, The Cochrane Library, Science Direct, Google Scholar and OpenGrey retrieved a total of 2190 results. Completion of the review is expected in late 2021.

Conclusions: This scoping review will be the first to map the extent of information regarding the genetic variants associated to the severity of COVID-19. The data gathered by this investigation could lead to biomarkers of severity in COVID-19 and the stratification of patients according to their genetic risk of disease severity.

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Authors

Estephania Candelo[1-3], Juan David Gutiérrez Medina[1-3], Andrés Gempeler[1], Harry Pachajoa[2-4]

[1]Fundación Valle del Lili, Centro de Investigaciones Clínicas, Cali, Colombia

[2]Universidad Icesi, Cali, Colombia

[3]Centro de Investigaciones en Anomalías Congénitas y Enfermedades Raras, CIACER, Cali, Colombia

[4]Fundación Valle del Lili, Departamento de Genética, Cali, Colombia

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Background: Coronavirus disease 19 (COVID-19), the disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is already responsible for more than four and a half million deaths worldwide. With a unique pathophysiology related to respiratory failure due to interstitial pneumonia and acute respiratory distress syndrome, severe COVID-19 is qualitatively different from moderate disease. Since genetics play a crucial role in susceptibility to viral infection and propensity to develop harmful inflammatory conditions, genetic heterogeneity promotes the question of whether gene variants might influence COVID-19 outcomes. The identification of genetic variants associated with severe courses of COVID-19 is a promising option for the improvement of prognostic tools, contemplation of new therapeutic targets and the development of patient's clinical risk stratification.

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Keywords: SARS-CoV-2; COVID-19; disease severity; genetic variant.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the 2020 pandemic of coronavirus disease (COVID-19). Up to January 28th, 2021 there were 100,200,107 confirmed cases and 2,158,761 deaths from COVID-19 worldwide [1]. The clinical spectrum of this

new disease ranges from asymptomatic and mildly symptomatic individuals who have a moderate upper respiratory tract infection, to severe COVID-19 which encompasses a harsh form of interstitial pneumonia caused, in part, by inflammatory injury affecting the lungs and lung blood vessels, which may require Intensive Care Unit (ICU) admission, mechanical ventilation and might increase the risk of multi-organ failure and death [2,3,4]. Therefore, critical COVID-19 is qualitatively different from moderate disease, for instance, among both there is a differential response to immunosuppressive therapy [5].

The risk for progression to the most aggressive form of COVID-19 is one of the most important aspects in the investigation of the clinical course of this disease [6]. Although the severity of COVID-19 has been associated with advanced age, high body mass index and obesity, and with comorbidities such as hypertension and diabetes mellitus [7,8]. It is possible these clinical factors do not account for the whole risk of disease progression.

Genetics play a crucial role in the two axes of critical COVID-19: susceptibility to viral infection and propensity to develop harmful inflammatory conditions [11]. For instance, susceptibility to the respiratory virus influenza is known to be associated with specific genetic variants (*e.g.,* SNPs in the IFITM3, GLDC and IL6 genes) [9]. Genome-wide association studies (GWAS) have allowed the identification of the 3p21.31 gene cluster as a genetic susceptibility locus in COVID-19 patients with respiratory failure [10]. The single-nucleotide polymorphism (SNP) rs11385942 at 3p21.31 comprises of six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1) which have functions potentially relevant to COVID-19 pathogenesis. Furthermore, genome-wide significant associations ($p < 5 \times 10^{-8}$) to critical course of COVID-19 at chr19p13.3, chr12q24.13 and chr21q22.1, involving gene clusters encoding antiviral restriction enzyme activators and interferon receptors, have also been reported [11]. Moreover, loss-of-function variants affecting essential immune processes could also be linked to the disease progression of COVID-19 regarding the pathophysiology of this condition: rare putative loss-of-function variants of X-chromosomal TLR7 gene, associated with impaired type I and II IFN responses, were identified in a case series of 4 young male patients with severe COVID-19 [14].

Accordingly, it is essential to identify biomarkers for stratification of patients at risk of developing severe disease due to SARS-CoV-2 infection. In this way, carrying early management, initiating support measures and application of treatments with potential benefits in the avoidance of the development of severe COVID-19 could have a great impact on the management, treatment, morbidity and mortality of this disease. The identification of genetic variants associated with a severe course of COVID-19 is a promising option to improve prognostic tools and propose new therapeutic targets.

A preliminary search in January 29th 2021 was conducted in Cochrane Database of Systematic Reviews, JBI Evidence Synthesis, PubMed, Science Direct and Web of Science and no current or underway scoping reviews on the topic of genetic variants and COVID-19 severity were identified. The objective of this scoping review is to assess the extent of the literature regarding the gene variants that could be associated with COVID-19 severity.

Review Question

The scoping review's primary research question is: "What is the knowledge status of the available literature on the existence of gene variants that might be associated with COVID-19 severity?"

Inclusion criteria

This scoping review is going to follow the inclusion criteria proposed by the Joanna Briggs Institute's Scoping Review Network [12]. Accordingly, this scoping review will consider observational studies and genome-wide association studies (GWAS) without discriminating in date or language. Additionally, systematic reviews that meet the inclusion criteria will also be considered. Furthermore, the population study criteria will be patients with severe COVID-19, defined as

hospitalized with respiratory failure and a confirmed SARS-CoV-2 viral RNA polymerase-chain-reaction (PCR).

Exclusion criteria

This scoping review will not consider any proper exclusion criteria.

Methods

The proposed scoping review will be conducted in accordance with the methodology from the Joanna Briggs Institute's Scoping Review Network [12] which is congruent with the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist for the correct development of scoping reviews [13].

Search strategy

The search strategy will focus on published studies without discriminating in date or language. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for the following databases: MEDLINE, LILACS, The Cochrane Library, Science Direct, Google Scholar and OpenGrey. Furthermore, a second search will be done to identify gray literature in the OpenGrey database. In order to identify the relevant articles, we established a systematic search strategy: ((("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh]) AND ("Polymorphism, Genetic"[Mesh] OR "Mutation"[Mesh] OR "Antibody Diversity"[Mesh] OR "Antigenic Variation"[Mesh]) AND ("Severity of Illness Index"[Mesh] OR "Death"[Mesh] OR "Critical Care"[Mesh] OR "Critical Illness"[Mesh] OR severity))). The search strategy will be adapted for each included database and/or information source but following the keywords mentioned before. For example, the key words for the Spanish search were the same (direct translation) according to DeCS (the structured scientific vocabulary index). The reference list of all included sources of evidence will be screened for additional studies.

Study/Source of Evidence selection

All identified citations will be collated and uploaded into Rayyan QCRI [15] and duplicates will be removed. Titles and abstracts will then be screened by three independent reviewers for application of selection criteria. Then, full text of selected citations will be assessed in detail to verify inclusion. Discrepancies will be resolved by consensus or by a third reviewer. Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram [13].

Data Extraction and Synthesis

The data extracted will include type of study, localization of the study, study objective (specific), study population, comorbidities of the studied population, sample size, biases, mutations, polymorphisms; type of variant, location, allele frequency, related phenotypes and prevalence. Any additional variables that will be relevant to the review question will be assessed in the final version of the scoping review. The data extraction tool will be used by two independent reviewers where data will be collected as categorical and continuous variants, which will be summarized as percentages for categorical variants and averaged with interquartile range for continuous variants. Moreover, characteristics and findings of the included studies will be summarized narratively. Internal validity of the study will be assessed by risk of bias tools available for each study design. Any disagreements that arise between the reviewers will be resolved through discussion. Any modifications will be detailed in the scoping review.

Results

The conducted search was performed on February 16th in MEDLINE, LILACS, The Cochrane

Library, Science Direct, Google Scholar and OpenGrey retrieved a total of 2190 results. Completion of the review is expected in late 2021.

Discussion

The clinical spectrum of COVID-19 is wide and includes asymptomatic patients, moderate infection of the upper respiratory tract, severe pneumonia with respiratory failure and even death. Due to the fact that the molecular pathways associated with severe SARS-CoV-2 infection are not clear, the identification of genetic differences among patients with severe and mild cases could generate genetic biomarkers that would aid to carry out a stratified management that positively impacts the prognosis of the patients worldwide.

Acknowledgments

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Conflicts of interest

The authors declare no conflict of interest related with this project.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
COVID-19: coronavirus disease
ICU: Intensive Care Unit
GWAS: genome wide association study
SNPs: single nucleotide polymorphisms
RNA: ribonucleic acid
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
LILACS: Literatura Latinoamericana y del Caribe en Ciencias de la Salud
DeCS: Descriptores en ciencias de la salud

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