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Genetic determinants associated with the progression of COVID-19 symptoms in diabetic patients: a systematic review protocol

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ABSTRACT. Diabetic patients have shown greater vulnerability, significant mortality, and serious complications when infected with SARS-CoV-2. Interindividual variation in susceptibility to severe progression of COVID-19 in diabetic patients has been associated with genetic polymorphisms. This systematic review protocol will critically synthesize the scientific evidence on the genetic polymorphisms of diabetic patients diagnosed with COVID-19 and will examine their impact on the progression of clinical symptoms and outcomes. This systematic review protocol was registered in PROSPERO under the number CRD42020181311. The protocol adheres to the PRISMA 2020 guidelines for reporting protocols. Searches will be performed in PubMed-NCBI /MEDLINE, EMBASE, Web of Science, Scopus, and Virtual Health Library databases using a comprehensive search strategy. Studies reporting the genetic polymorphisms of diabetic patients infected with SARS-CoV-2 and its correlation with the clinical outcome will be included. Study selection, data extraction, methodology quality assessment, and strength of evidence assessments will be conducted by two

reviewers independently. The results will be presented as association of genetic determinants with disease progression in diabetic patients infected with SARS-CoV-2. The objective is to determine the genetic polymorphisms that significantly impact the clinical symptoms of COVID-19 in diabetic patients, to help guide disease prognosis and treatment approach.

Key words: COVID-19; SARS-CoV-2; Coronavirus; Genetic Polymorphism; Diabetes Mellitus

INTRODUCTION

The World Health Organization (WHO) announced on March 11, 2020, that the outbreak of "COronaVIrus Disease of 2019" (COVID-19), which initially started in Asia, had become a pandemic (Asselah et al., 2021). The pandemic caused by the SARS-CoV-2 virus, unexpectedly impacted much of the world, especially Brazil. Different clinical conditions are manifested in people diagnosed with the virus, from asymptomatic to necessary support with invasive mechanical ventilation (IMV) and intensive care, causing uncertainties in managing the disease progression risks (Alhazzani et al., 2020).

The different clinical pictures depend on interactions between four factors: (1) the severity of the infection (viral variant); (2) the host response (age, sex, health conditions, inter-individual genetic differences,, and comorbidities) (Xie and Chen, 2020); (3) the patient's ventilatory response capacity to hypoxemia and (4) the time elapsed between the onset of the disease and follow-up and observation by the health team (Gattinoni et al., 2020).

The interaction of these factors leads to highly phenotypic heterogeneity of COVID-19, with a wide spectrum of clinical symptoms (Chung et al., 2020), from the absence of symptoms to mild and moderate symptoms and the progression to hypoxemia and severe pneumonia with acute respiratory distress syndrome associated with an exacerbated inflammatory state known as "cytokine storm", which is the leading cause of multiple organ failure (Sardu et al., 2020). The main comorbidities, hypertension, cardiovascular diseases, lung and kidney disease, vitamin D (VD) deficiency, obesity, and diabetes mellitus (DM) were identified as pre-existent conditions for severe progression in COVID-19 (Figueroa-Pizano et al., 2021).

DM is one of the major metabolic disorders globally and is a polygenic disease, with high morbidity and mortality indices. In association with DM, COVID-19 has an even worse development and expressive prevalence of admission to intensive care units (ICU) and the need for IMV support. The United States had the highest prevalence rates of diabetes and/or uncontrolled hyperglycemia in people hospitalized for COVID-19, approximately 12% to 30%, while in Latin America, DM was reported in 8.3% of cases of COVID-19 (Bode et al., 2020). DM patients have shown greater vulnerability when compared to those who did not have this comorbidity. It was observed that patients with DM had a higher mortality rate and more severe complications (Figueroa-Pizano et al., 2021).

Diabetes affects the immune system and can impair the body's ability to fight infections, including viral diseases like COVID-19. Diabetes may also affect the health of blood vessels and lead to endothelial dysfunction, which combined with COVID-19-induced vascular damage, may contribute to the severity of the disease. Elevated blood glucose levels can adversely affect the immune response, increase inflammation, and impair lung function, all of which may contribute to the progression of COVID-19 symptoms (Sardu et al., 2020; Bode et al., 2020; Williams et al., 2020; Karaderi et al., 2020; Figueroa-Pizano et al., 2021).

Studies show that among patients who survived COVID-19, regardless of the clinical form, but especially those who had prolonged hospitalization in both the ICU and hospital wards, 80% evolved into a complex association of cognitive, psychological and motor symptoms, which was called “Post-COVID-19 Syndrome” (do Prado et al., 2022). In this context, decreased quality of life, increased dependence on other people for personal care and poor performance during activities of daily living are the main consequences (Delbressine et al., 2021)

Genetic studies presented a panel of genes and their functions relevant to susceptibility to SARS-CoV-2 (Karaderi et al., 2020; Sayed, 2021), others through variations of the Single Nucleotide Polymorphisms (SNPs) or insert/deletion polymorphisms reaffirmed the pathophysiology of disease in patients with comorbidities (Gunal et al., 2021; Calabrese et al., 2021), differences of allele frequencies among Europeans and Asians for a specific risk polymorphism were shown (Srivastava et al, 2020). Some studies already demonstrate an association between genetic polymorphisms and the severity of COVID-19 disease (Martínez-Gómez et al., 2022; Qu et al., 2022; Sabater et al., 2022) while other studies did not observe this association (Alimoradi et al., 2022).

The goal of this systematic review is to evaluate genetic variations to know the profile of genetic risk of patients with DM infected by SARS-CoV-2 and their relationship with the progression of symptoms of the disease. We will assess DNA sequences, SNPs, or insert/deletion polymorphisms, to elucidate whether genetic polymorphisms are associated with the progression of COVID-19 symptoms in diabetic patients. This proposed systematic review will answer the following questions:

• Why do some patients with diabetes mellitus, when infected by SARS-CoV-2, have a worse progression of symptoms of COVID-19?

• What genetic polymorphisms are associated with the progression of the symptoms of COVID-19 in diabetes mellitus patients?

Despite a preponderance of evidence that diabetes is associated with poor COVID-19 outcomes, there is a lack of information on inpatient glycemic control among patients with diabetes and acute hyperglycemia those hospitalized with COVID-19. A direct correlation with clinical outcomes has not been established (Bode et al., 2020). Moreover, the development of COVID-19 may also result from a complex interaction between the microbial, environmental, and host genetic components. The complex relationship between diabetes and COVID-19 mortality is often mistaken for other mortality risk factors in people with COVID-19, including the genetic factors that define pro-inflammatory states, high blood pressure levels, and hyperglycemia

(Williams et al., 2020). Therefore, this protocol presents an opportunity to deliver a systematic review that will yield a comprehensive synthesis for understanding the genetic determinants associated with the progression of COVID-19 symptoms in diabetic patients.

MATERIAL AND METHODS

The protocol was developed following the PRISMA for Systematic Review Protocols (PRISMA-P) 2015 and considered references such as the Cochrane Handbook for Systematic Reviews of interventions and the Joanna Briggs Institute (JBI) reviewer's manual (Figure 1). Our review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration) under the number CRD42020181311.

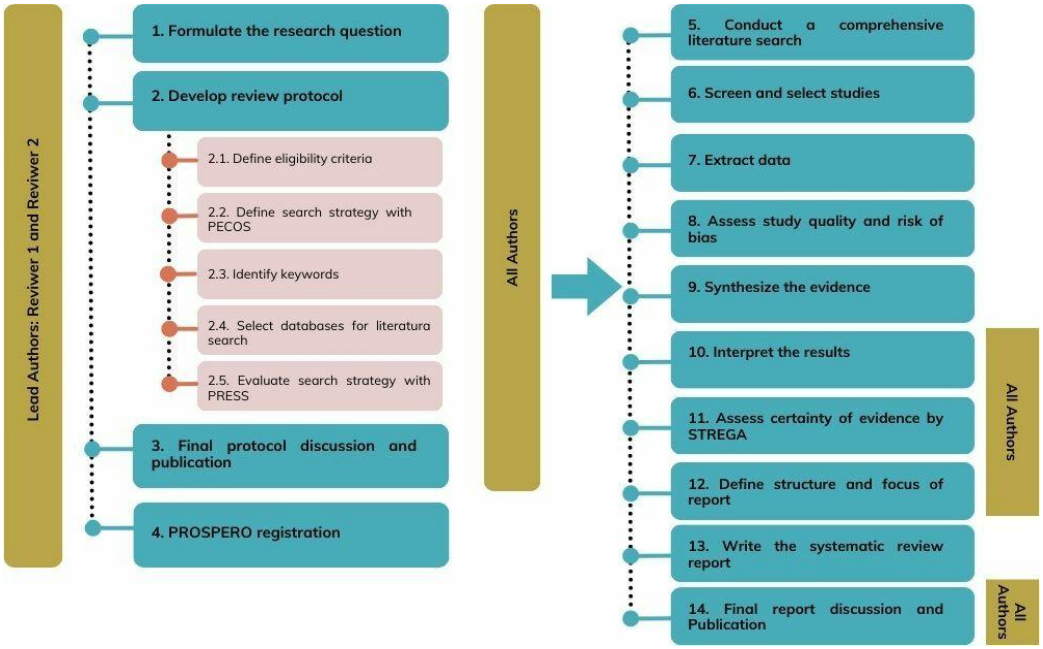

Figure 1. Flowchart illustrating the design of the systematic review of the genetic determinants of diabetic patients that are associated with the progression of COVID-19 symptoms.

Eligibility Criteria

All original observational, cohort or case-control studies on genetic polymorphisms in COVID-19 in the DM population will be eligible. To formulate the search strategy, we adopted the PECOS acronym, designed for systematic reviews of etiology and risk factors (Mooa et al., 2020). Details of the inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and exclusion criteria for determining genetic polymorphisms associated with disease progression in diabetic patients infected with SARS-CoV-2.

PECOS acronym	Inclusion criteria	Exclusion criteria
P—Patient/ Population	Adults with DM who had COVID-19.	Studies conducted with non-diabetic populations. Non-human studies including in vitro observations or research concentrating on animal experiments.
E—Exposure	Genetic polymorphisms.	Studies without data on genetic polymorphisms.
C—Control or Comparison	Adults with DM who had COVID-19 and were asymptomatic.	None.
O—Outcomes	Development of mild, moderate, or critical symptoms of COVID-19 and their complications (Based NIH) Clinical Spectrum of SARS-CoV-2 Infection). Death will be the second outcome.	Studies without or with insufficient data on of symptoms and progression of COVID-19.
S—Study design	Observational studies the cohort type or case control, original research publications, no restriction language, published from 31 December 2019 to 30 November 2023.	Reviews, case studies, governmental and non-government reports, unpublished studies, grey literature, and opinion letters.

Information sources

For each selected database, the literature search strategies was created by identifying subject-specific header indexes (e.g., MeSH terms, Emtree terms, and DeCS-Health Science Descriptors) along with their synonyms (keywords) and additional terms. The search terms were combined using the Boolean operators 'AND' and 'OR' (Lefebvre et al., 2020).

The searches will be performed in five online databases (Pubmed/NCBI, EMBASE, Web of Science, SCOPUS, Virtual Health Library (BVS)). The information from these five databases will be collected from the date of COVID-19 emergence (December 31, 2019, to November 30, 2023). In cases where literature cannot be accessed through database filters, manual searching will be conducted using the Google Scholar Search Engine. The snowball searching technique will be employed during manual searching to identify relevant publications related to our literature of interest. Furthermore, references of eligible studies obtained through both manual and database searches will be examined to ensure comprehensive coverage of pertinent publications.

Two independent reviewers (LCS and KdFS) will evaluate the search strategy following the Peer Review of Electronic Search Strategies (PRESS) (Shamseer et al., 2015). No language or status restrictions will be applied, but publication period and human subjects will be included.

Search strategy

To enhance methodological transparency and facilitate the reproducibility of the findings, the search strategy will be implemented in accordance with the PRISMA-P checklist) (Shamseer et al., 2015). The search strategy will focus solely on key terms aligned with a pre-established PECOS acronym. The search filtering mechanisms in the databases will be the dates from December 31, 2019, to November 30, 2023, and human

studies. For manual search, the title (Genetic Polymorphism and COVID-19) will be written directly in Google Scholar and will be included in the list of articles that were not identified by the database screening.

The references of the included studies will be investigated so that the availability of not included and valuable literature is present. In addition, PROSPERO will be searched for ongoing or recently completed systematic reviews, as relevant studies are identified, reviewers will check cited articles and may include relevant citations.

Any potential modifications to the protocol will be documented in the final report publication, which will adhere to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The search strategy combining MeSH terms and keywords used in the MEDLINE/PubMed preliminary pilot search strategy Table 2; it will be adapted to meet the specific syntax requirements of each database.

Table 2. Preliminary pilot search strategy in MEDLINE/PubMed-NCBI.

DATABASE	SEARCH STRATEGY
MEDLINE /PubMed-NCBI	#1((“COVID-19” [MeSH Terms]) OR "COVID 19" [All Fields] OR "SARS-CoV-2 Infection" [All Fields] OR "Infection, SARS-CoV-2" [All Fields] OR "SARS CoV 2 Infection" [All Fields] OR "SARS-CoV-2 Infections" [All Fields] OR "2019 Novel Coronavirus Disease" [All Fields] OR "2019 Novel Coronavirus Infection" [All Fields] OR "2019-nCoV Disease" [All Fields] OR "2019 nCoV Disease" [All Fields] OR "2019-nCoV Diseases" [All Fields] OR "Disease, 2019-nCoV" [All Fields] OR "COVID-19 Virus Infection" [All Fields] OR "COVID 19 Virus Infection" [All Fields] OR "COVID-19 Virus Infections" [All Fields] OOR "Virus Infection, COVID-19" [All Fields] OR "Coronavirus Disease 2019" [All Fields] OR "Disease 2019, Coronavirus" [All Fields] OR "Coronavirus Disease-19" [All Fields] OR "Coronavirus Disease 19" [All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" [All Fields] OR "SARS Coronavirus 2 Infection" [All Fields] OR "COVID-19 Virus Disease" [All Fields] OR "COVID 19 Virus Disease" [All Fields] OR "Disease, COVID-19 Virus" [All Fields] OR "Virus Disease, COVID-19" [All Fields] OR "2019-nCoV Infection" [All Fields] OR "2019 nCoV Infection" [All Fields] OR "2019-nCoV Infections" [All Fields] "Infection, 2019-nCoV" [All Fields] OR "COVID19" [All Fields] OR "COVID-19 Pandemic" [All Fields] OR "COVID 19 Pandemic" [All Fields] OR "Pandemic, COVID-19" [All Fields] OR "COVID-19 Pandemics" [All Fields] OR "SARS-CoV-2 variants" #2"diabetes"[All Fields]) OR "diabetes mellitus" [All Fields]) OR “Complications of Diabetes Mellitus” [All Fields]) OR “Diabetes Complication” [All Fields]) OR “Diabetes Mellitus Complication” [All Fields]) OR “Diabetes Mellitus Complications” [All Fields]) OR “Diabetes Related Complications” [All Fields]) OR “Diabetes-Related Complication” [All Fields]) OR “Diabetes-Related Complications” [All Fields]) OR “Diabetic Complication” [All Fields]) OR “Diabetic Complications” #3“polymorphism” [All Fields] OR “polymorphism genetic” [All Fields]) OR “Amplified Fragment Length Polymorphism Analysis” [All Fields]) OR “Polymorphism, Single-Stranded Conformational” [All Fields]) OR “Polymorphism, Restriction Fragment Length” [All Fields]) OR “Polymorphism, Single Nucleotide” [All Fields]) OR “DNA Copy Number Variations” #4= #1 AND #2 AND #3 Filters: Full text, Humans, from 2019 - 2023

Study Selection

The primary screening, utilizing the predetermined search terms, manual searches, and reference searches. This will be followed by independent verification from other team members. To ensure a systematic and thorough search, Mendeley bibliographic software will be employed to store, organize, and manage all references. The studies will be selected independently by two reviewers using Rayyan software.

The consecutive screening and checking processes are implemented to ensure the selection of high-quality manuscripts and minimize the risk of overlooking important

literature. If there are any discrepancies among the reviewers, all authors will collaborate to address the differences through discussions or by reviewing the full-text articles for clarification. However, if a consensus cannot be reached regarding the inconsistencies, an external reviewer will be consulted to resolve the matter. The original published papers that satisfy the eligibility criteria will be considered in the final report.

Screening

The acquired literature will be imported into Mendeley bibliographic software to screen titles and abstracts. Duplicate documents and studies not meeting the predefined inclusion criteria will be excluded. Two reviewers will independently assess the titles and abstracts of the studies. If there is a substantial agreement among the reviewers (at least 80%), each reviewer will thoroughly assess the complete articles. If the agreement falls below 80%, the articles will be re-evaluated, and any discrepancies will be discussed and resolved through consensus. If a disagreement persists, a third reviewer (RSS) will utilize the Rayyan app to make the final decision. Upon reviewing the full text of the remaining studies, the final selection of included studies will be determined.

After reading the full text of the other studies, the final studies included will be determined. When the full text is unavailable, contact with authors will be attempted twice via email to obtain further information. Studies with no full text available will be excluded. Neither of the review authors will be blind to the journal titles, study authors, or institutions. The entire study selection process will be shown in a PRISMA flowchart (Figure 2) (Page et al., 2020).

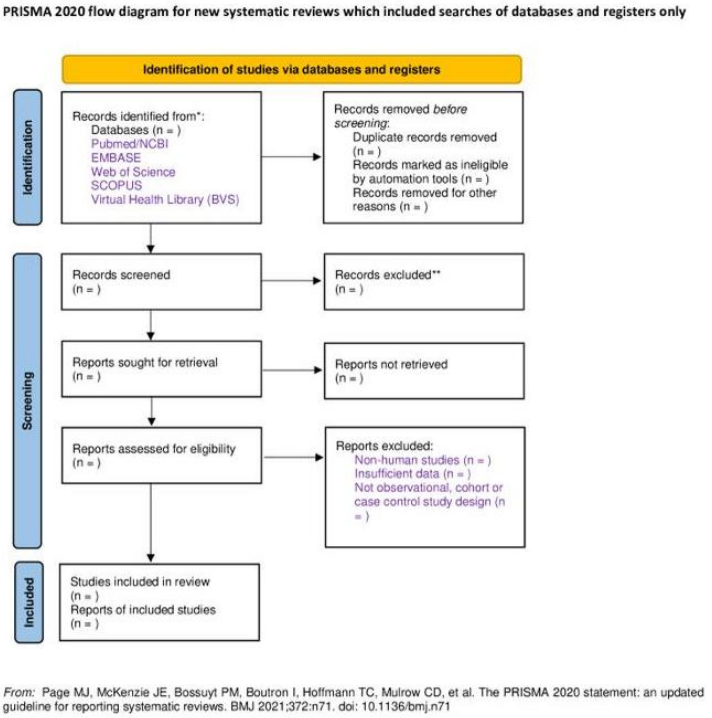

Figure 2. PRISMA flowchart for the study selection process.

Risk of methodological bias

The risk of methodological bias will be assessed through a critical tool formulated by the JBI for or case control studies (Supplementary material 1) (Moola et al., 2020). This tool has 11 questions that must be answered with "Yes", "No", "Unclear" or "Not applicable". Studies that answer "Yes" to more than 60% of the questions will be classified as low risk of bias.

Two independent reviewers (LCS and KdFS) will assess methodological bias. A third reviewer (RSS) will perform data synthesis, and discrepancies will be resolved by consensus between the reviewers. The results of the evaluation of bias in the studies will be shown as a graph. Furthermore, bias assessment will not be used as an exclusion criterion for studies.

STREGA (Strengthening the Reporting of Genetic Association) will be the tool used to assess the quality of genetic association studies, as well as to mitigate publication bias. We emphasize that heterogeneity in studies is predicted through population diversity, study design, and genotyping methods, among others.

Data extraction

Data extraction will be performed by two independent reviewers (LCS and KdFS), and the reviewers will resolve disagreements by discussion with referees RSS) will judge the unresolved disputes. We will use Rayyan to assist and optimize the study screening process and perform a quantitative analysis of the data extracted from selected articles and prepared in Microsoft® Excel.

The extracted data will include study characteristics, methodology, genetic characteristics, clinical picture manifested during COVID-19 and all-important results for the studied groups. Contact with authors will be attempted twice via email to obtain further information to resolve any uncertainties observed. Studies without or with insufficient data on symptoms and progression of COVID-19 will be excluded.

The official nomenclature of genes, genomic location, and polymorphisms will be verified in the National Center for Biotechnology Information (NCBI) database at Gene (https://www.ncbi.nlm.nih.gov/gene) and SNP (https://www.ncbi.nlm.nih.gov/snp/) sections.

Data synthesis

The information extracted will be as follows: Study characteristics (reference, year of publication, country where the study was performed and study design), Genetic characteristics (gene, genomic location, genotyping method, investigated polymorphism; type of polymorphism; size of the sample of case and control groups, genotypic or allelic comparison performed and their frequencies for the groups), Genetic models (allelic, recessive, dominant, codominant and overdominant), Clinical condition (symptoms manifested in the disease, ex. asymptomatic, mild or critical symptoms), and Association measures (odds ratio and p-value).

Initially, a narrative synthesis of the findings of the included studies will be provided, structured around the Patient, Exposure, Comparators, Outcome and Study Design (PECOS) method. In this synthesis, we will use graphs to better visualize the findings.

Measures of treatment effect

Genetic association studies with sufficient data on alleles and genotypes will be grouped according to each polymorphism to calculate odds ratios (OR) with a 95% confidence interval (CI).

If there is a significant number of homogeneous studies, a meta-analysis will be performed using the Stata Software 12.0. If possible, a meta-analysis will be applied to each genetic polymorphism to determine the 95% ORs and CIs cluster.

The results grouped in all five genetic models (allelic, recessive, dominant, codominant and overdominant) will be calculated. In addition, a sensitivity analysis will be conducted, excluding each study individually to detect the effects on the stability of the combined results and the source of heterogeneity.

The heterogeneity will be calculated by the inconsistency index $I^{2,}$ which can quantify heterogeneity ranging from 0% (no heterogeneity) to 100% (differences between effect sizes can be completely explained by chance alone), and the percentage interpretations are as follows: for an I2 value close to 25% low heterogeneity, close 50% moderate heterogeneity and close to or grather than 75% hight heterogeneity (Higgins et al., 2003). According to the Cochrane review guidelines, a value of P 0.10 for the Q test should be interpreted as indicative of the absence of heterogeneity between studies; in this case, a combined OR will be estimated using a random effects model (DerSimonian and Laird method); otherwise, a fixed-effect model (using the Mantel-Haenszel method) will be used. Meta-analysis can lead to a false positive or negative conclusion. Therefore, if possible, we will use the trial sequential analysis (TSA) to reduce these statistical errors.

Forest plots and funnel plots graphs will be presented if the meta-analysis is performed after the heterogeneity analysis. Publication bias will be explored through a visual inspection of the funnel plot and Egger's test.

Patient and public involvement

As this is a systematic review protocol, no patients or public will be involved.

DISCUSSION

To the extent that we have explored all the previously published systematic reviews, a systematic review focused on the genetic alterations of diabetic patients and their associations with the different clinical conditions and outcomes presented by this population has not yet been performed. Summarizing different research results that

addressed different phenotypes is the basis for understanding and making evidence-based clinical decisions.

This systematic review protocol comprehensively describes the entire review process, including the data search and extraction strategy. The review encompasses various steps, namely identification, study inclusion, data extraction, and data synthesis, ensuring a thorough examination of the included studies and their characteristics.

However, the pooling of data for meta-analysis poses challenges due to the expected substantial heterogeneity among studies. This heterogeneity arises from factors such as extensive genetic variability, participant characteristics, and diverse outcomes.

Therefore, this systematic review will provide relevant evidence; the primary outcomes will be used to trace genetic polymorphisms associated with worse disease progression in patients with DM infected by COVID-19, as well as identify the genetic polymorphisms with a potential biomarker to predict the future development of serious complications of COVID-19 in patients with DM.

Finally, we will identify the main allelic frequencies of greater risk associated with the worst outcome of COVID-19 in patients with DM, thus providing evidence for monitoring action health professionals from different countries, especially those with greater accessibility to perform the genetic profile of patients for precision interventions.

AUTHOR CONTRIBUTIONS

Conceptualization: AASR, RSS. Formal analysis: LCS, KFS, AASR, RSS. Methodology: LCS, JSC, KFS, AASR, RSS. Resources: LCS. Software: LCS. Supervision: AASR, RSS. Writing – original draft: LCS, AASR, RSS.

FUNDING

This research received no external funding.

DATA AVAILABILITY STATEMENT

No extra data is available besides the attached file since it is a protocol for systematic reviews.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Alhazzani W, Moller MH, Arabi YM, Loeb M, et al. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 46(5): 854-887.

Alimoradi N, Sharqi M, Firouzabadi D, Sadeghi MM, et al. (2022). SNPs of ACE1 (rs4343) and ACE2 (rs2285666) genes are linked to SARS-CoV-2 infection but not with the severity of disease. *Virol. J*. 19(1): 48.

Asselah T, Durantel D, Pasmant E, Lau G, et al. (2021). COVID-19: Discovery, diagnostics and drug development. *J. Hepatol*. 74(1): 168-184.

Bode B, Garrett V, Messler J, McFarland R, et al. (2020). Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. *J. Diabetes Sci. Technol*. 14(4): 813-821.

Calabrese C, Annunziata A, Coppola A, Pafundi PC, et al. (2021). ACE Gene I/D Polymorphism and Acute Pulmonary Embolism in COVID19 Pneumonia: A Potential Predisposing Role. *Front Med*. 7: 631148.

Chung M, Bernheim A, Mei X, Zhang N, et al. (2020). CT imaging features of 2019 novel coronavirus (2019-NCoV). *Radiology*. 295(1): 202-207.

Do Prado CB, Emerick GS, Cevolani Pires LB and Salaroli LB (2022). Impact of long-term COVID on workers: A systematic review protocol. *PLoS ONE*. 17(9): e0265705.

Delbressine JM, Machado FVC, Goe¨rtz YMJ, Van Herck M, et al. (2021). The Impact of Post-COVID-19 Syndrome on Self-Reported Physical Activity. *Int. J. Environ. Res. Public Health*. 18(11): 6017.

Figueroa-Pizano MD, Campa-Mada AC, Carvajal-Millan E, Martinez-Robinson KG, et al. (2021). The underlying mechanisms for severe COVID-19 progression in people with diabetes mellitus: a critical review. *AIMS PUBLIC Heal*. 8(4): 720-742.

Gattinoni L, Chiumello D, Caironi, Busana M, et al. (2020). COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 46(6): 1099-1102.

Gunal O, Sezer O, GU U, CE O, et al. (2021). Angiotensin-converting enzyme-1 gene insertion/deletion polymorphism may be associated with COVID-19 clinical severity: A prospective cohort study. *Ann. Saudi Med*. 41(3):141-146.

Higgins JP, Thompson SG, Deeks JJ and Altman DG (2003). Measuring inconsistency in meta-analyses. *BMJ*. 327(7414): 557-60.

Karaderi T, Bareke H, Kunter I, Seytanoglu A, et al. (2020). Host Genetics at the Intersection of Autoimmunity and COVID-19: A Potential Key for Heterogeneous COVID-19 Severity. *Front. Immunol*. 11: 586111.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, et al. (2019). Searching for and selecting studies. Cochrane *Handb. Syst. Rev. Interv*. Chapter 4, p.67–107.

Martínez-Gómez LE, Herrera-López B, Martinez-Armenta C, Ortega-Peña S, et al. (2022). ACE and ACE2 Gene Variants Are Associated With Severe Outcomes of COVID-19 in Men. *Front Immunol*. 13: 812940.

Moola S, Munn Z, Tufanaru C, Aromataris E, et al. (2020). Explanation of Analytical Cross Sectional Studies Critical Appraisal. *JBI Man. Evid. Synth*. 1-5. Available: [https://joannabriggs.org/critical_appraisal_tools]

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, et al. (2020). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021: 372:n71. doi: 10.1136/bmj.n71.

Qu HQ, Qu J, Glessner J and Hakonarson H (2022). Mendelian randomization study of obesity and type 2 diabetes in hospitalized COVID-19 patients. *Metabolism*. 129: 155156.

Sabater MM, Nicolás RE, Bendicho AI, Vázquez EG, et al. (2022). Polymorphisms in ACE, ACE2, AGTR1 genes and severity of COVID-19 disease. *PLoS One*. 17(2): e0263140. doi: 10.1371/journal.pone.0263140.

Sardu C, Gambardella J, Morelli MB, Wang X, et al. (2020). Hypertension, thrombosis, kidney failure, and diabetes: Is covid-19 an endothelial disease? a comprehensive evaluation of clinical and basic evidence. *J. Clin. Med*. 9(5): 1417. doi: 10.3390/jcm9051417.

Sayed S (2021). COVID-19 and diabetes; Possible role of polymorphism and rise of telemedicine. *Prim. Care Diabetes*. 15(1): 4-9.

Shamseer L, Moher D, Clarke M, Ghersi D, et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 349: g7647

Srivastava A, Bandopadhyay A, Das D, Pandey RK, et al. (2020). Genetic Association of ACE2 rs2285666 Polymorphism With COVID-19 Spatial Distribution in India. *Front Genet*. 11: 564741. doi: 10.3389/fgene.2020.564741.

Williams DM, Nawaz A and Evans M (2020). Diabetes and Novel Coronavirus Infection: Implications for Treatment. *Diabetes Ther*. 11(9): 1915-1924.

Xie M and Chen Q (2020). Insight into 2019 novel coronavirus — An updated interim review and lessons from SARS-CoV and MERS-CoV. *Int. J. Infect. Dis*. 94: 119-124.