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Pharmacogenetics and pharmacogenomics in COVID-19

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ABSTRACT

Objective: To analyze the relationship between pharmacogenetics and pharmacogenomics with Covid-19. **Methods:** This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using the PubMed and SciELO databases. Case, observational and bench studies in English and Portuguese were included, from December 2019 to December 2022. **Results:** Population genetic differences influence the effects of drugs on Covid-19. Studies highlight the importance of considering metabolic disorders, such as diabetes and dyslipidemia, as risk factors. The pharmacogenetic interaction between medications for these disorders and treatments for Covid-19 must be evaluated. Genetic polymorphisms, such as GNB3 c.825C>T, present conflicting results, indicating the complexity of genetic interactions. Other studies analyze genes such as ACE2, CYP2C19 and variants in IFITM3, revealing associations and challenges in interpreting results. **Final considerations:** This review highlights that population genetic distinctions influence the severity of Covid-19 and the response to pharmacological treatments. Polymorphisms in specific genes show varying results, indicating the need for more comprehensive studies. The use of medicines still lack evidence for the management of Covid-19 as it may present risks to patients, highlighting the importance of pharmacogenetics and pharmacogenomics in personalizing treatments.

Keywords: Pharmacogenetics, COVID-19, COVID-19 drug treatment.

RESUMO

Objetivo: Analisar a relação entre farmacogenética e farmacogenômica com a Covid-19. **Métodos:** Esta revisão sistemática seguiu as diretrizes Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), utilizando as bases de dados PubMed e SciELO. Foram incluídos estudos de caso, observacionais e de bancada em inglês e português, de dezembro de 2019 a dezembro de 2022. **Resultados:** As diferenças genéticas populacionais influenciam os efeitos dos medicamentos na Covid-19. Estudos destacam a importância de considerar distúrbios metabólicos, como diabetes e dislipidemia, como fatores de risco. A interação farmacogenética entre medicamentos para esses distúrbios e tratamentos para a Covid-19 deve ser avaliada. Polimorfismos genéticos, como GNB3 c.825C>T, apresentam resultados conflitantes, indicando a complexidade das interações genéticas. Outros estudos analisam genes como ACE2, CYP2C19 e variantes do IFITM3, revelando associações e desafios na interpretação dos resultados. **Considerações finais:** Esta revisão destaca que as distinções genéticas populacionais influenciam a gravidade da Covid-19 e a resposta aos tratamentos farmacológicos. Polimorfismos em genes específicos apresentam resultados variados, indicando a necessidade de estudos mais abrangentes. O uso de medicamentos ainda carece de evidências

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para o manejo da Covid-19, pois pode apresentar riscos aos pacientes, destacando a importância da farmacogenética e da farmacogenômica na personalização dos tratamentos.

Palavras-chave: Farmacogenética, COVID-19, Tratamento farmacológico da COVID-19.

RESUMEN

Objetivo: Analizar la relación entre farmacogenética y farmacogenómica con Covid-19. **Métodos:** Esta revisión sistemática siguió las pautas de Elementos de informes preferidos para revisiones sistemáticas y metanálisis (PRISMA), utilizando las bases de datos PubMed y SciELO. Se incluyeron estudios de caso, observacionales y de banco en inglés y portugués, desde diciembre de 2019 hasta diciembre de 2022. **Resultados:** Las diferencias genéticas poblacionales influyen en los efectos de los medicamentos sobre el Covid-19. Los estudios destacan la importancia de considerar los trastornos metabólicos, como la diabetes y la dislipidemia, como factores de riesgo. Se debe evaluar la interacción farmacogenética entre los medicamentos para estos trastornos y los tratamientos para el Covid-19. Los polimorfismos genéticos, como GNB3 c.825C>T, presentan resultados contradictorios, lo que indica la complejidad de las interacciones genéticas. Otros estudios analizan genes como ACE2, CYP2C19 y variantes en IFITM3, revelando asociaciones y desafíos en la interpretación de los resultados. **Consideraciones finales:** Esta revisión destaca que las distinciones genéticas poblacionales influyen en la gravedad de Covid-19 y la respuesta a los tratamientos farmacológicos. Los polimorfismos en genes específicos muestran resultados variables, lo que indica la necesidad de estudios más completos. El uso de medicamentos aún carece de evidencia para el manejo de Covid-19, ya que puede presentar riesgos para los pacientes, lo que destaca la importancia de la farmacogenética y la farmacogenómica en la personalización de los tratamientos.

Palabras clave: Farmacogenética, COVID-19, Tratamiento farmacológico de COVID-19.

INTRODUCTION

Covid-19, caused by the RNA virus SARS-CoV-2, and manifests in humans with more general initial symptoms, such as fever, cough and fatigue, and then proceeds to more aggressive symptoms, such as shortness of breath and difficulty breathing, which can lead to the need for intubation, neurological manifestations, cardiac complications, as well as a generalized inflammatory condition due to the cytokine storm (CAFIERO C, et al., 2020).

Patients with the severe form of the disease, defined by SpO2 < 94%, PaO2/FiO2 < 300 mm Hg, respiratory rate > 30 breaths/min or pulmonary infiltrates > 50%, develop an immune response associated with an increased abundance of pro-inflammatory cytokines and chemokines, including IL1β, IL6, IL8, TNFα, MIP1α and VEGF, which characterizes the "cytokine storm". In addition to respiratory problems, patients with severe Covid-19 suffer complications that involve target organ damage, such as acute myocardial injury, renal failure, abnormal liver function and liver failure, as well as sepsis and disseminated intravascular coagulation; therefore, the mortality rate in this pathology varies according to the patient's clinical and demographic condition (KARAMI H, et al., 2021).

The pandemic caused by SARS-CoV-2 has triggered a serious global health problem, with an extreme need for advances in the area of health, starting with the development of vaccines and the search for pharmacological treatment to combat its different symptoms, its complications and the virus itself. Various drugs have already been used, such as hydroxychloroquine and azithromycin, and their use was based on hypotheses and empirical tests, without there necessarily being scientific proof of their efficacy. As a result, a wide range of treatments was generated, which had negative, positive or neutral effects, with different responses in patients and population (KALIL AC, et al., 2020).

In this regard, the pharmacogenomics and pharmacogenetics approaches have gained prominence, since the former allows the identification and characterization of genetic profiles that influence the pharmacokinetics and pharmacodynamics of the drugs used to treat SARS-CoV-2, especially with regard to genes that encode drug metabolizing enzymes, transporters and receptors (FRANCZYK B, et al., 2022). The second would be the modulation of the response to a drug by a change in a single genetic marker, obtaining information on changes in a single gene capable of significantly influencing the response to a particular drug (SHASTRY BS, 2022).

These two areas of study make it possible to understand how individual and population genetic variability influences or modifies the response to a drug, according to alterations and patterns present in the genome, as well as making it possible to identify possible genetic targets and mechanisms that can be explored for treatments.

Based on the understanding of genetic and genomic variability in responses to drug therapy, modulating the individual or collective response to a given drug, it becomes possible to choose effective drugs together with favorable genotypes for a good prognosis of the disease. Thus, the aim of this study is to carry out a systematic bibliographic survey on the relationship between pharmacogenetics and pharmacogenomics with Covid-19, seeking to better clarify the genetic and genomic influence on the response to drugs used to combat the disease.

METHODS

Type of study

The present study refers to a systematic literature review, following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (TETZLAF J, et al., 2021), and it was registered in OSF Registries platform as a project (DOI 10.17605/OSF.IO/G2DVR).

Databases used and research method

The PubMed and SciELO databases were used as search tools, adopting the “free full texts” search filter in the aforementioned databases. Regarding descriptors and Boolean operators, the following were adopted: (COVID-19) OR (SARS CoV 2) AND (PHARMACOGENETICS) AND (PHARMACOGENOMICS).

Eligibility Criteria

Open access studies were included, which were case, observational and bench studies, that addressed the proposed topic, originals in English and Portuguese existing in the PubMed and SciELO databases from December 2019 to December 2022. Studies that did not address the proposed topic, stories, letters, editorials, reports, comments, duplicates, unavailable articles, opinion articles, review articles or articles written in languages other than English and Portuguese.

In this way, each study was analyzed in full in search of an answer to the question: “What is the relationship between pharmacogenetics and pharmacogenomics with Covid-19?”, drawn up based on the PICO (Patient/Problem, Intervention, Comparison and Outcomes) strategy (SANTOS C. M. DA C, et al., 2007)

Selection process

From the selected articles, a more careful analysis was made regarding which ones would be used as a basis for the research. The pre-selected documents were divided equally among five reviewers, applying the inclusion and exclusion parameters determined in the research and thus defining their usefulness for the study.

Risk of bias analysis

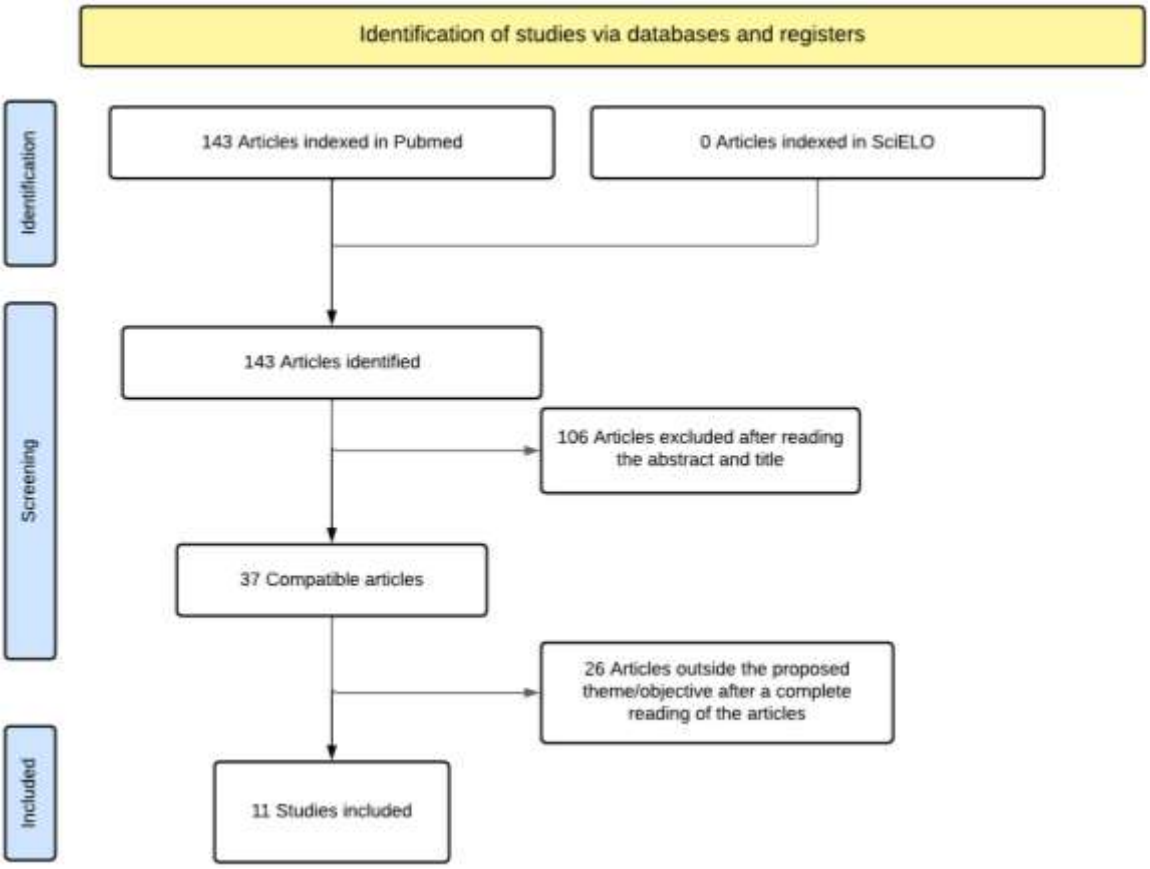
To analyze the risk of bias, the Newcastle-Ottawa tools were used for longitudinal articles and Joanna Briggs Institute tools for cross-sectional articles (WEELS G, et al.; MOOLA J, et al., 2017). Then, tables were created to represent the results of this evaluation.

RESULTS

143 articles were found using the initial search method. 106 articles were excluded after reading the titles and abstracts, with 37 articles being selected for full reading. The result of this process was the inclusion of 11 studies that met the selection criteria. **Figure 1** shows the article selection process, and Table 1 shows the main information in the articles found.

As for the risk of bias, the Newcastle-Ottawa tool showed that most of the longitudinal studies were considered to be of good quality and had a low risk of bias (**Table 2**). As for the cross-sectional studies, the Joanna Briggs tool showed that most of the studies were considered to be of good quality and with a low risk of bias (**Table 3**).

Figure 1 – Prisma Flowchart.



Source: Berni LC, et al., 2024.

Table 1 - Articles included in the study.

N	Author (year)	Objective	Methods	Main results
1	Sahana, et al., (2021)	To study the extent of drug–gene (PGx), drug–drug interaction (DDI) and drug–drug–gene interactions (DDGI) associated with COVID-19 infection in the Indian population.	The genome sample of 1,029 individuals, obtained by the IndiaGen project, and a list of 89 drugs used for COVID-19, obtained from the PharmGKB and DrugBank databases, were used to understand the extent of drug-gene (pharmacogenetics), drug-drug and drug-drug-gene interactions associated with COVID-19 therapy in the Indian population.	Ribavirin is associated with the IFNL3, IFNL4, ITPA and VDR genes, with genetic variations such as IFNL3 rs12979860 and IFNL4 rs8099917, present in 37% of the population analyzed, causing the drug to be less effective. The Indian population also shows a reduced response to Lopinavir due to genetic variations. The ABCC4 gene is associated with a lower response to Ibuprofen and Remdesivir in 1% of the population, affecting the transport and metabolism of the latter.
2	Strafella, et al., (2020)	To investigate the distribution of genetic variations in IL6 and IL6R genes in order to find candidate prognostic and pharmacogenetic biomarkers for COVID-19 and neuroinflammatory diseases	The study analyzed 271 DNA samples from the Italian population in search of genetic variations. It used methods such as array comparative genomic hybridization (aCGH) and whole exome sequencing (WES), with analysis of copy number variations (CNVs) and single nucleotide variants (SNVs) in specific genes such as the ones	It was found that genetic alterations, such as the rs190436077 variant, which, although uncommon, causes changes in the structure of proteins, affecting the response to drugs that interact with the IL6 and IL6R. This can compromise the effectiveness of these drugs in treating COVID-19 and its complications.

			related to IL6 and IL6R. In addition to exploring their association with diseases such as COVID-19.	
3	Tuteja, et al., (2022)	To identify patients with Covid-19 that may be susceptible to remdesivir-associated liver injury	Million Veteran Program, a large multi-ethnic genetic biobank, was used to collect information on 4125 patients who were hospitalized with COVID-19 between March 15, 2020, and June 30, 2021. 1,697 patients received remdesivir and 2,428 did not for control. Participants of non-Hispanic White (NHW) and non-Hispanic Black (NHB) populations were included in the analysis. Participants were genotyped using a custom axiom genotyping platform and imputed using the 1000 Genomes reference panel. Pharmacogene phenotypes were assigned using Stargazer. Linear regression was performed on peak log-transformed enzyme values, stratified by population, adjusted for age, sex, baseline liver enzymes, comorbidities, and 10 population-specific principal components.	Non-Hispanic white (NHW) patients with intermediate/weak metabolic (IM/PM) genetic variants in the CYP2C19 gene showed a 9% increase in maximum ALT levels under remdesivir treatment, compared to participants with normal/fast/ultrafast (NM/RM/UM) variants, association that was not seen in non-Hispanic black (NHB) patients. Additional analyses, focusing only on remdesivir-treated patients, confirmed that CYP2C19 IM/PM variants were linked to 13% increases in peak ALT levels in NHW participants, but had no effect in NHB.
4	Castanha, et al., (2022)	To analyse the complement and antibody response to SARS-CoV-2 in hospitalized patients	Plasma levels of key complement markers, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, and antibodies against SARS-CoV-2 and seasonal human common cold coronaviruses (CCCs) were measured in hospitalized patients with COVID-19 of moderate (n = 18) and critical severity (n = 37), as well as in healthy controls (n = 10).	The complement system is associated with the severity of Covid-19, with high levels in ICU patients. There was a significant reduction in C3, C5 levels were reduced, while C5a and sC5b-9 were elevated in the ICU. This suggests a crucial role for complement in the immune response, related to pro-inflammatory cytokines and worse clinical outcomes, such as higher mortality and prolonged length of stay.
5	Qin, et al., (2021)	To identify a new drug for combination therapy and to improve the survival rate of CRC patients infected with COVID-19.	The genes associated with colorectal cancer (CRC) were identified from the Cancer Genome Atlas Database (TCGQ), and genes associated with Covid-19 were identified from the Online Mendelian Inheritance in Man (OMIM) and National Center for Biotechnology Information (NCBI) databases. Then, the CRC and COVID-19-associated genes were overlaid to determine the predisposing genes of CRC/ COVID-19.	Two clusters of genes involved in immune response (IL1A, IL2, and IL6R) and cell proliferation (CCND1, PPARG, and EGFR) mediated by biochanin A in CRC/COVID-19 condition were identified, serving as a treatment for CRC and preventing the cytokine storm from Covid-19
6	Schönfelder, et al., (2021)	To analyze the role of SNPs in the gene IFITM3 in SARS-CoV-2 infection.	Genotyping of the SNPs rs12252 and rs34481144 in the gene IFITM3 was performed in 239 SARS-CoV-2-positive and 253 SARS-CoV-2-negative patients. The association of the SNPs with susceptibility to SARS-CoV-2 infection and severity of COVID-19 was analyzed.	No association regard the SNPs in the gene IFITM3 was found for an increased risk of SARS-CoV-2 infection. Only a multivariable analysis pointed to a relationship between male gender and predisposition to COVID-19 severity

7	Möhlendick, et al., (2022)	To analyze whether the single-nucleotide polymorphism (SNP) rs5443 in the gene GNB3, might be a suitable biomarker to predict T cell responses and the outcome of COVID-19	The influence of demographics, pre-existing disorders, laboratory parameters at the time of hospitalization, and the GNB3 rs5443 genotype in a comprehensive cohort (N = 1570) on the outcome of COVID-19 was analyzed. In a sub-cohort, SARS-CoV-2-specific T cell responses and associated GNB3 rs5443 genotypes were analyzed.	The rs5443 genotype was significantly associated with protection against Covid-19 fatality. Younger patients (<62 years), with erythrocyte (≥4.0/nl); platelet (≥133.5/nl); neutrophil (<6.6/nl), and lymphocyte (≥0.9/nl) counts above these thresholds remained predictors of protection from Covid-19 fatality.
8	Lopardo, et al., (2022)	To study the influence of sex on the course of infection and the differences in prognostic markers between genders in COVID-19 patients	64 patients with PCR-proven SARS-CoV-2 infection were recruited: n = 34 men (median age 66, range 32–90), and n = 30 women (median age 65, range 20–95). BPIFB4 plasma levels were determined using a human long palate, lung, and nasal epithelium carcinoma-associated protein 4 (C20orf186) ELISA kit (Cusabio CSBYP003694H). There was a division between patients with oxygen saturation between 90% and 94% who did not need treatment in the ICU, considered to have a mild to moderate COVID-19, and patients with oxygen saturation below 90% who needed to go to the ICU, considered to be of severe intensity disease	There was an inverse relationship between the concentration of BPIFB4 protein and the severity of the disease in men, with individuals with severe Covid-19 having less BPIFB4 and vice versa. Meanwhile, the same relationship was not found in women
9	Fang, et al., (2021)	To identify potential drug therapeutic targets from the high-throughput data of virus-infected organoids and cells and explore if there are clinical drugs in use that can target the infectious protein	Two datasets related to COVID-19 (GSE150819 and GSE147507) were downloaded. By analyzing the high throughput expression matrix of uninfected human bronchial organoids and infected human bronchial organoids in GSE150819, 456 differentially expressed genes (DEGs) were identified, which were mainly enriched in the cytokine-cytokine receptor interaction pathway and similar pathways. The protein-protein interaction (PPI) network of DEGs was also constructed to identify the hub genes. Subsequently, GSE147507, containing lung adenocarcinoma cell lines (A549 and Calu3) and the primary bronchial epithelial cell line (NHBE), was analyzed, yielding 799, 460, and 46 DEGs, respectively.	The results showed that in human bronchial organoids, A549, Calu3 and NHBE samples infected with SARS-CoV-2, only one positively regulated CSF3 gene was identified. Furthermore, no satisfactory results were obtained regarding the investigation of Elbasivir and Ritonavir, which act on CSF3
10	Čiučiulkaitė, et al., (2022)	To investigate if the immune response after vaccination against COVID-19 is influenced by genotypes of the c.825C>T polymorphism in the gene GNB3 (rs5443)	In the main study group, 204 participants were analyzed 1 and 6 months after the second vaccination with mRNA-1273 regarding the measure of antibodies against the SARS-CoV-2 spike protein and T-cell responses against a peptide pool of SARS-CoV-2 S1. Furthermore,	A increased T-cell immune response to SARS-CoV-2 was noticed in the CC genotype carriers of the GNB3 c.825C>T polymorphism after vaccination, thus, indicating a better protection mediated by T-cell against COVID-19

			1 month after the second vaccination with mRNA-1273, antibodies against the SARS-CoV2 spike protein were measured within a group of 597 participants. All participants were identified with genotypes of GNB3 c.825C>T.	
11	Möhlendick, et al., (2021)	To study whether single nucleotide polymorphisms (SNPs) in the ACE2 and ACE genes can alter the binding or entry of SARS-CoV-2 and increase tissue damage in the lung or other organs.	Genotyping of SNPs in the ACE2 and ACE genes was carried out in 297 patients who tested positive for SARS-CoV-2 and 253 who were negative for SARS-CoV-2, and the association of SNPs with susceptibility to SARS-CoV-2 infection and the severity of COVID-19 was analyzed from this context	The GG genotype of the SNP Angiotensin-Converting Enzyme 2 (ACE2) rs2285666 may be associated with greater susceptibility to SARS-CoV-2 infection and the severity of COVID-19, along with factors such as male gender and cardiovascular disease. The study found no significant association between COVID-19 and the ACE gene, or with the use of drugs that inhibit it (ACEi), or with angiotensin receptor blockers.

Source: Berni LC, et al., 2024.

Table 2 - Risk of Bias: Newcastle-Ottawa tools.

N	Studies (Cohort	Representativeness of the exposed cohor	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
1	Castanha, et al., (2022)		*	*	*	**	*	*	*	8*
2	Schönfelder, et al., (2021)	*	*	*	*	*	*	*	*	8*
3	Möhlendick, et al., (2022)	*		*		**	*	*	*	7*
4	Čiučiulkaitė, et al., (2022)		*	*	*	*	*	*	*	7*
5	Möhlendick, et al., (2021)	*	*	*	*	*	*	*	*	8*
N	**Studies (Case-Control)**	**Is the case definition adequate?**	**Representativeness of the cases**	**Selection of Controls**	**Definition of Controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-Response rate**	Total
1	Tuteja et al. (2022)	*	*	*	*	**	*	*	*	9*

Source: Berni LC, et al., 2025.

Table 3 - Risk of Bias: Joanna Briggs Institute tools

N	Studies (Cross-sectional)	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
1	Sahana et al. (2020)	YES	YES	YES	YES	YES	YES	YES	YES
2	Strafella et al. (2020)	YES	YES	YES	YES	NO	NO	YES	YES
3	Qin et al. (2021)	YES	YES	YES	YES	NO	NO	YES	NO
4	Lopardo et al. (2022)	YES	YES	YES	YES	NO	NO	YES	YES
5	Fang et al. (2021)	YES	YES	YES	YES	NO	NO	YES	YES

Source: Berni LC, et al., 2025.

The study by by Sahana, et al. (2021) analyzed the influence of pharmacogenomics on the therapies used for Covid-19 in the Indian population. They used a genome sample of 1029 individuals, obtained from the IndiaGen project, and a list of 89 drugs used for Covid-19, obtained from the PharmGKB and DrugBank databases. As a result, it was observed that Ribavirin's effect is associated with the IFNL3, IFNL4, ITPA and VDR genes, with variations in the IFNL3 rs12979860 and IFNL4 rs8099917 polymorphisms, which are responsible for the lower response to this drug, being present in around 37% of the Indian population.

The gene related to the increase in the plasma concentration of Lopinavir is also reduced in this population. The ABCC4 gene had its variation related to the lower response to Ibuprofen and Remdesivir, the latter being related to its impaired transport and metabolism in 1% of this population. The analysis of hydroxychloroquine also showed that the CYP2D6, CYP2C8 and SLCO1A2 genes, which are related to its transport and metabolism, are impaired in the group evaluated, which adds to the negative nature of its various adverse effects.

In the same study, it was observed that a significant proportion of the drugs used for Covid-19 share genes with drugs used to treat metabolic disorders, i.e. they have interactions relating to the drug's target proteins, metabolizing enzymes and transporters/loaders. In this context, considering the most prescribed drugs used in Covid-19 cases, 45% interacted with lipid-lowering drugs, 34% with those used to treat hypertension, 49% with anticoagulants, antiplatelets and fibrinolytics, and 59% with antidiabetics.

The investigation of genetic variations by Strafella C, et al. (2020), based on 271 DNA samples from the Italian population, points to modifications in genes related to IL6 (Interleukin 6) and ILR6 (Interleukin 6 receptor) as a factor of interest for analyzing Covid-19 with its various symptoms and complications, especially neuroinflammation. This study highlighted genetic alterations such as the rs190436077 variant which, although rare, is responsible for protein structural changes, which modifies the response of possible drugs that target this complex, impairing their desired effects in cases of Covid-19 and its complications.

The study by Tuteja S, et al (2022) explored the impact of treatment with remdesivir on patients hospitalized with Covid-19, as part of the Million Veteran Program. The study involved 4,125 participants, of whom 1,697 received remdesivir and 2,428 did not. Patients on remdesivir had distinct characteristics, such as advanced age, high body mass index (BMI), higher Charlson comorbidity index and higher baseline levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Treatment with remdesivir lasted an average of 4 days. In the remdesivir-treated group, peak ALT and AST levels were higher compared to the untreated group. Specifically, 21.5% of patients on remdesivir had a marked increase in ALT, exceeding three times the normal upper limit, compared to 10.2% of those not treated. The analysis revealed that treatment with remdesivir was associated with increases of approximately 30% in maximum ALT values and 16% in maximum AST values, after taking into account baseline levels and differences between populations.

A genetic exploration in this same study identified that non-Hispanic white (NHW) patients, those with intermediate/weak metabolic (IM/PM) genetic variants in the CYP2C19 gene, showed a 9% increase in maximum ALT levels under remdesivir treatment, compared to participants with normal/fast/ultrafast (NM/RM/UM) variants. This association, however, was not seen in non-Hispanic black (NHB) patients.

Additional analyses, focusing only on remdesivir-treated patients, confirmed that CYP2C19 IM/PM variants were linked to 13% increases in peak ALT levels in NHW participants, but had no effect in NHB. The study by Priscila, et al. (2022) investigated adult patients with Covid-19, evaluating demographic and clinical variables and plasma samples. The study included patients hospitalized in intensive care units (ICU) and exclusive wards (non-ICU) for Covid-19.

The presence of the SARS-CoV-2 virus was confirmed through polymerase chain reaction (PCR) tests with positive results, using nasopharyngeal swab samples. In addition to the Covid-19 patients, a control group made up of plasma samples from healthy adults (healthy controls [HCs]) before the pandemic (n=10) was included as a reference for measuring complement proteins.

Samples from patients who participated in the University of Pittsburgh Acute Lung Injury Registry (n=15), admitted to the ICU due to acute respiratory illness but negative for SARS-CoV-2, were also analyzed. The results of the study of Priscila, et al. (2022) indicated a correlation between the activation of the complement system and the severity of Covid-19.

Complement activation, which is fundamental to the immune response, was shown to be increased in ICU patients compared to non-ICU patients. This study investigated the genetic relationship between complement system activation and disease severity in Covid-19 patients. A marked reduction in plasma C3 levels was observed in ICU patients, suggesting an increase in C3 consumption in severe cases of Covid-19.

In addition, levels of C3a, a cleavage product of C3, were considerably elevated in patients with Covid-19, especially in those in critical condition, indicating an exacerbated activation of the complement system during infection. Similarly, C5 levels were significantly reduced in ICU patients, while C5a levels and the C5a/C5 ratio were notably increased. The elevated presence of sC5b-9, an activation product of the terminal complement cascade, was also observed in Covid-19 patients.

These findings suggest that the complement system plays an important role in the aggravated immune response during Covid-19 infection, particularly in critical cases. In addition, high levels of complement activation were linked to pro-inflammatory cytokines, such as IL-6 and IL-8, as well as clinical markers of inflammation, such as procalcitonin.

These findings suggest that complement activation may contribute to systemic inflammation and the exacerbated immune response in severe cases of Covid-19. A relationship was also observed between high complement activation and worse clinical outcomes, including higher 90-day mortality and prolonged hospitalization. This underscores the clinical relevance of complement activation in Covid-19 and highlights its potential as a prognostic indicator for disease progression. The study by Qin J, et al. (2021) focused on patients with Colorectal Cancer (CRC) infected with Covid-19.

The aim was to look for combined treatment alternatives with improved survival rates, including Biochanin A, an O-methylated isoflavone from the flavonoid class, which promotes apoptosis in cancer cells and there is evidence that it can protect the lung against toxicity and injury. From the Cancer Genome Atlas Database (TCGQ) they identified the genes associated with CRC, and from the Online Mendelian Inheritance in Man (OMIM) and National Center for Biotechnology Information (NCBI) databases they identified genes associated with Covid-19.

They then identified 144 genes shared between CCR/Covid-19 and 212 genes associated with Biochanin A, and overlapped the CCR/Covid-19 genes, revealing 13 potential Biochanin A targets. The aim was to attack 2 target groups: cell proliferation genes (CCND1, PPARG and EGFR) and inflammatory genes (IL1A, IL2 and IL6R), serving as a treatment for CRC and preventing the cytokine storm from Covid-19. However, it is worth noting that the findings were based on network pharmacology and bioinformatics, and there was no clinical or biological study.

The study by Schönfelder K, et al. (2021) focused on determining whether single nucleotide polymorphisms (SNPs) in the IFITM3 gene, a gene that inhibits the hemifusion of the viral membrane between the host and the cytoplasm of the viral cell, are related to severe Covid-19 cases and susceptibility. The SNPs rs12252 and rs34481144 were genotyped in 2 groups, one composed of 239 Covid-19 positive patients with at least 1 positive result (RT-PCR) and the other of 253 symptomatic but Covid-19 negative patients via RT-CPR. However, no association was found for an increased risk of SARS-CoV-2 infection, with only a multivariable analysis showing a relationship between male gender and predisposition to Covid-19 severity.

The study by Mohlendick B, et al. (2022) mainly analyzed the rs5443 polymorphism in the GNB3 gene together with the influence of demographic data such as pre-existing disorders and laboratory parameters at the time of hospitalization on the severity of Covid-19. A total of 1,570 patients tested positive for SARS-CoV-2. Genomic DNA was extracted from the blood of each patient. Hematological parameters (erythrocyte, platelet, neutrophil and lymphocyte counts) and medical history about pre-existing comorbidities of the

cardiovascular system (e.g. myocardial infarction, coronary heart disease, but not hypertension) were also documented for each patient. In addition, in the same study, the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immuno-inflammation index (SII) were also calculated as inflammatory markers.

The study found that the rs5443 genotype was significantly associated with protection against the fatality of Covid-19 since carriers with this genotype had it at very similar frequencies, except for those who had the "fatal" outcome of the disease. Next, when the analysis was carried out to assess the influence of pre-existing comorbidities, hematological parameters and inflammatory markers, it was found that younger patients (<62 years), with erythrocytes (≥4.0/nl); platelets (≥133.5/nl); neutrophils (<6.6/nl), and lymphocytes (≥0.9/nl) with counts above these thresholds remained predictors of protection against Covid-19 fatality.

In addition, the study by Lopardo V, et al. (2022) lists an explanation for the greater severity of the coronavirus in men, with BPIFB4 (bactericidal/permeability-increasing fold-containing family-B-member-4) being the one investigated. The role of BPIFB4 in this disease is to mitigate the damaging effects on the cells of the human body and the inflammatory effects caused by the virus.

This protein, which belongs to innate immunity, is found in the respiratory epithelium, upper airways, respiratory secretions, hematopoietic tissue and mononucleated cells. It has age-related anti-inflammatory properties and is found in high levels in long-lived individuals, giving them a protective character, justifying its investigation in the role related to Covid-19 and the response between genders.

Since BPIFB4 has proven immunomodulatory functions, after analyzing individuals infected with Covid-19, an inverse relationship was found between the concentration of this protein and the severity of the disease in men, i.e. in individuals with severe Covid-19 there is less BPIFB4 and vice versa. However, the same was not found in women, both in the context of Covid-19 and in other pathological and even physiological situations. In this way, this protein can help predict the degree of involvement that a male individual may develop (LOPARDO V, et al., 2022).

In the study carried out by Fang C et al., (2021) it was observed that the CSF3 (Colony-Stimulating Factor 3) gene was the only one, among those studied, with the highest expression in human organoid bronchi affected by Covid-19 and is the most modulated. This gene participates in granulopoiesis, hematopoietic stem cell migration and neutrophil function.

Therefore, due to its greater modulation in bronchi, it should be considered as a target for pharmacological research. The research investigated drugs such as Elbasvir and Ritonavir, which act on CSF3, but no satisfactory results were obtained. In addition, the study by Čiučiulkaitė et al. (2022) analyzed the GNB3 c.825c>T gene and its impact on the adaptive response against SARS-CoV-2.

The gene has TT, CC and CT polymorphisms; the most relevant finding was that the CC modification increased the response to the Covid-19 vaccine 6-fold 1 month after the first dose. The gene was chosen for the research because there were already records of its influence on increasing the humoral response after vaccination against Hepatitis B. Thus, the study points to a possible reduction in Covid-19 damage in those who have the CC-type polymorphism.

The study by Möhlendick et al. (2021), in which 297 patients who tested positive for SARS-CoV-2 and 253 patients who tested negative for SARS-CoV-2 were included and analyzed, suggests that the GG genotype of the Single Nucleotide Polymorphism (SNP) Angiotensin-Converting Enzyme 2 (ACE2) rs2285666 may be associated with greater susceptibility to SARS-CoV-2 infection and the severity of Covid-19, in addition to factors such as male gender and cardiovascular disease. ACE2 is a membrane-anchored angiotensin II-converting enzyme whose binding to the spike (S) protein is essential for the virus to enter the cell.

In addition, another frequently discussed gene is ACE, which encodes the angiotensin-converting enzyme (ACE), generally responsible for cleaving angiotensin I (Ang I) into Ang II, which activates the angiotensin II type 1 receptor (AT1R), mediating vasoconstrictive, pro-inflammatory and fibrogenic effects (MÖHLENDICK B, et al., 2021). However, the study found no significant association between Covid-19 and this gene, nor with

the use of drugs that inhibit it (ACEi), or with angiotensin receptor blockers (ARBs) (ČIUČIULKAITĖ B, et al., 2022). As for the risk of bias, it should be noted that the study did not represent the general population, since the patients were highly selected and included those who were seriously ill with or without SARS-CoV-2.

DISCUSSION

It is possible to see that genetic differences in populations are an influencing factor in the effects of the drugs administered in Covid-19 cases. In this sense, the genetic specificities noted in the Indian population, with impaired biological responses to ibuprofen, remdesivir and hydroxychloroquine in Covid-19, are compared to the genetic differences in the Italian population in view of possible modifications to the response of drugs targeting Interleukin 6 (IL6) and its receptor (ILR6) in the disease (SAHANA S, et al., 2021 and STRAFELLA C, et al., 2020). The existing literature supports the idea of population genetic differences, which have already been studied in order to promote a better understanding when establishing a therapeutic approach (ZHOU Y.; LAUSCHKE V. M., 2021)

It is known that metabolic disorders such as diabetes and dyslipidemia are already considered risk factors for more severe Covid-19 (WANG J, et al., 2022). In addition, drugs used to combat Covid-19 and drugs adopted for these metabolic disorders trigger their actions on the same genes for therapeutic response, which includes sharing target proteins, transporters and metabolic enzymes, with consequent pharmacological interactions.

In this way, it is possible to see that not only are these metabolic disorders contributing factors to a more severe Covid-19 condition, but also the medications used to treat these diseases play a role in altering the expected effects of pharmacological therapies in the treatment of Covid-19, which can jeopardize the prognosis of the disease. Therefore, given this context of pharmacogenetic interaction, the drugs used in these metabolic-based diseases should be evaluated in patients with diabetes, hypertension and dyslipidemia before pharmacological treatment for Covid-19 is established (SAHANA S, et al., 2021).

Among the pharmacogenomic targets analyzed in this article, the genes Colony Stimulating Factor (CSF3), Guanine Nucleotide-binding protein beta-3 (GNB3 c.825 C>T) and Bactericidal Permeability Increasing Protein Fold Containing Family B Member 4 (BPIFB4), which may be linked to biological responses to Covid-19, have limitations such as a lack of in-depth studies, and BPIFB4 showed no evidence of becoming a pharmacological target, but rather a characteristic possibly linked to shorter life expectancy in men in general and not exactly related to Covid-19.

The polymorphism related to GNB3 c.825C>T refers to the vaccine response to the action of antibodies, but there is a need for long-term follow-up to analyze the real impact of this information on the progression of the disease. The CSF3 gene was the most promising due to its upregulation in respiratory tissue in the presence of SARS-CoV-2, and has been identified as a response to potential drugs (LOPARDO V, et al., 2022; FANG C, et al., 2021; ČIUČIULKAITĖ, et al., 2021).

However, according to Noske GD et al. (2023), due to the high number of mutations in the SARS-CoV-2 virus, it is currently difficult to find an effective drug against the disease. Other studies point to antivirals that act directly on coronavirus target proteins, such as M^{pro} (main protease), or monoclonal antibodies, such as Sotrovimab, which acts against the virus's Spike protein and blocks its binding and consequent entry into human cells (FERREIRA, LLG and ANDRICOPULO AD, 2020; ZHENG B, et al., 2022). Both require more effective studies and tests with a longer time frame.

The study by Tuteja S et al. (2022) offers a valuable contribution to understanding the effects of remdesivir in hospitalized Covid-19 patients, with a particular focus on ethnic and genetic differences. This study presented an in-depth analysis of the effects of remdesivir treatment concerning alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, as well as the influence of specific genetic variants of the Cytochrome P450 Protein 2C19 (CYP2C19) gene on these effects. The results of this study highlight the need for careful evaluation of liver effects in patients treated with remdesivir, particularly in specific ethnic

populations and in individuals with certain genetic variants. The identification of an association between CYP2C19 IM/PM genetic variants and increased ALT levels in NHW patients underlines the importance of considering genetic factors in determining individual response to remdesivir.

Furthermore, the lack of effect observed in NHB patients indicates the complexity of genetic and ethnic interactions that can influence treatment response. These findings have important clinical implications, highlighting the need for a personalized approach to the administration of remdesivir, with more careful consideration of liver risks in patients with certain genetic variants. Furthermore, the studies highlight the importance of additional research that further explores the interactions between genetics, ethnicity and response to remdesivir, in order to inform a more precise and effective approach to treating Covid-19 (TUTEJA S, et al., 2022).

The study by Priscila et al. (2022) offers valuable insights into the crucial role of the complement system in the exacerbated immune response during SARS-CoV-2 infection. The results of this study highlight the importance of understanding the interaction between the complement system and the immune response during Covid-19 infection. Identifying complement activation as a potential prognostic indicator may inform more precise management and treatment strategies, targeting therapy to modulate complement activation and reduce systemic inflammation in patients with severe COVID-19.

Furthermore, these findings highlight the need to consider therapies targeting the complement system as a potentially effective therapeutic approach to reduce disease severity and improve clinical outcomes in patients with Covid-19. However, further studies are needed to fully elucidate the specific mechanisms by which the complement system contributes to the pathogenesis of Covid-19 and to develop more targeted and effective therapeutic strategies.

Studies not only into the role of specific nucleotide polymorphisms such as rs5443 in the GNB3 gene, but also other polymorphisms in various genes are still scarce, and their mechanisms have yet to be clarified. Concerning the rs5443 nucleotide of the GNB3 gene, some studies have shown results that may conflict with the claim that this gene is a protector against a worse Covid-19 prognosis since it has already been associated with higher risks of cardiovascular events (PEITZ T, et al., 2022; LI HL, et al., 2016).

However, it is well established that SARS-CoV-2 disease has several phenotypes whose clinical severity is directly linked to risk factors, such as being overweight or cardiovascular disease - and that genetic modulations can be protective or worsening mechanisms. In this sense, the difference between individuals may be due to innate immunity (GUTIÉRREZ-BAUTISTA JF, et al., 2022).

In the study by Möhlendick B et al. (2021), while the GG genotype of ACE2 rs2285666 and the G allele appeared to be associated with a higher risk of infection, the reason behind this association remains unknown. The ACE rs1799752 D/I polymorphism did not affect the evolution of Covid-19, contrary to what was observed in a recent Spanish study of Gómez J, et al. (2022), which recorded an increased risk of an unfavorable Covid-19 outcome in carriers of the ACE DD genotype.

However, in the German study of Möhlendick B et al. (2021), the G allele of ACE2 rs2285666 was associated with a three times greater risk of unfavorable Covid-19 outcome. The study suggests that an imbalance between ACE and ACE2 may play a central role in Covid-19, with decreased ACE2 activity during SARS-CoV-2 infection. This may explain the association of the A allele of ACE2 with a possible protective role, as carriers of this allele can better cope with the detrimental effects of increased Ang II levels (MÖHLENDICK B, et al., 2021).

The results of the study by Qin J et al. (2021) suggest that biochanin A may be a promising candidate as an adjuvant therapy in the treatment of patients with Covid-19 and colorectal cancer. Biochanin A acts on specific pathways, such as the interaction of cytokines with receptors, the PI3K-Akt signaling pathway and the JAK-STAT signaling pathway, which play crucial roles in the immune response and carcinogenesis of colorectal cancer. In addition, studies have linked the genes identified (IL1A, IL2, IL6R, CCND1 and EGFR) to colorectal cancer, highlighting their importance.

In the study by Schönfelder K et al. (2021), the results indicate no significant relationship between the rs12252 and rs34481144 polymorphisms in the IFITM3 gene with susceptibility to SARS-CoV-2 infection or the severity of Covid-19 in this cohort study with German patients. However, it is worth noting that the research was carried out in Germany, with mostly Caucasian people, so its findings may not be directly applicable to populations of different ethnic origins. Therefore, research into the role of these genetic variants in SARS-CoV-2 infections still requires studies in larger and more diverse cohort studies.

FINAL CONSIDERATIONS

This review shows that population genetic differences are factors that not only influence the clinical severity of Covid-19 but are also relevant to the effects of the drugs used for treatment. Therefore, not only the patient's profile concerning metabolic diseases are risk factors for the disease. Different results have been shown in relation to polymorphisms present in specific nucleotides in the GNB3 gene, the polymorphism related to c.825C>T referring to the vaccine response related to antibody activity has not shown clarity about better or worse prognosis due to the lack of long-term follow-up to quantify the real impacts. However, the polymorphism in the rs5443 nucleotide of the same gene was associated with protection against the worse prognosis of Covid-19. The other studies involving genetic variations in CYP2C19 IM/PM and ACE rs1799752 D/I in association with pharmacological therapies also do not show clear results to their benefit, and some of these interactions, such as the use of remdesivir, which had adverse effects with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) indices, showed that the use of drugs still lack evidence for the management of Covid-19 and may present risks to patients.

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