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Gene 844 (2022) 146790

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Systematic review and meta-analysis of human genetic variants contributing to COVID-19 susceptibility and severity

Kajal Gupta [1], Gaganpreet Kaur [1], Tejal Pathak [1], Indranil Banerjee [*]

Cellular Virology Lab, Department of Biological Sciences, Indian Institute of Science Education and Research, Mohali (IISER Mohali), Sector 81, S.A.S Nagar, Mohali 140306, India

ARTICLE INFO

Edited by: X. Carette

Keywords:
SARS-CoV-2
COVID-19
Meta-analysis
Systematic review
Polymorphism
Association

ABSTRACT

The COVID-19 pandemic has spawned global health crisis of unprecedented magnitude, claiming millions of lives and pushing healthcare systems in many countries to the brink. Among several factors that contribute to an increased risk of COVID-19 and progression to exacerbated manifestations, host genetic landscape is increasingly being recognized as a critical determinant of susceptibility/resistance to infection and a prognosticator of clinical outcomes in infected individuals. Recently, several case-control association studies investigated the influence of human gene variants on COVID-19 susceptibility and severity to identify the culpable mutations. However, a comprehensive synthesis of the recent advances in COVID-19 host genetics research was lacking, and the inconsistent findings of the association studies required reliable evaluation of the strength of association with greater statistical power. In this study, we embarked on a systematic search of all possible reports of genetic association with COVID-19 till April 07, 2022, and performed meta-analyses of all the genetic polymorphisms that were examined in at least three studies. After identifying a total of 84 studies that investigated the association of 130 polymorphisms in 61 genes, we performed meta-analyses of all the eligible studies. Seven genetic polymorphisms involving 15,550 cases and 444,007 controls were explored for association with COVID-19 susceptibility, of which, *ACE1* I/D rs4646994/rs1799752, *APOE* rs429358, *CCR5* rs333, and *IFITM3* rs12252 showed increased risk of infection. Meta-analyses of 11 gene variants involving 6702 patients with severe COVID-19 and 8640 infected individuals with non-severe manifestations revealed statistically significant association of *ACE2* rs2285666, *ACE2* rs2106809, *ACE2* rs2074192, *AGTR1* rs5186, and *TNFA* rs1800629 with COVID-19 severity. Overall, our study presents a synthesis of evidence on all the genetic determinants implicated in COVID-19 to date, and provides evidence of correlation between the above polymorphisms with COVID-19 susceptibility and severity.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has wreaked havoc on global public health by claiming millions of lives and posing unprecedented challenges to world economy and healthcare systems. While SARS-CoV-2 is highly contagious, its clinical manifestation differs substantially in magnitude, varying from asymptomatic or mildly symptomatic to critical illness and death (Wu and McGoogan, 2020 Apr 7). Among the infected individuals with symptoms, majority suffered mild illness, 14 % developed severe disease, and 5–6 % progressed to critical stage requiring intensive care or mechanical ventilation support (Verity et al., 2020; Wang et al., 2021 Mar 8; Epidemiology Working., 2020). As the COVID-19 pandemic unfolded, one of the key

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; HIV, Human immunodeficiency virus; RSV, Respiratory syncytial virus; HTLV-1, Human T-lymphotropic virus-1; HPV, Human papillomavirus infection; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HSV, Herpes simplex virus; EPV, Epstein-barr virus; GWAS, Genome-wide association studies; SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; HWE, Hardy-Weinberg equilibrium; ICU, Intensive care unit; RAS, Renin-angiotensin system; LDL, Low density lipoprotein; IL, Interleukin; PCR, Polymerase chain reaction; RT-PCR, Real time PCR; ARMS, Amplification refractory mutation system; RFLP, Restriction fragment length polymorphism; STA, Specific target amplification.

* Corresponding author.
E-mail address: indranil@iisermohali.ac.in (I. Banerjee).

[1] Contributed equally.

https://doi.org/10.1016/j.gene.2022.146790
Received 18 May 2022; Received in revised form 25 July 2022; Accepted 5 August 2022
Available online 17 August 2022

questions that baffled clinicians and scientists is why some individuals develop severe, often life-threatening complications, while others suffer mild illness or have no symptoms. However, extraordinary research response to COVID-19, both at organizational and individual levels, rapidly illuminated the disease mechanism and identified the risk factors that disproportionately contribute to severe disease progression. Although individuals of all ages are at risk of contracting SARS-CoV-2, aged individuals ($\geq$ 60 years of age) and patients with underlying comorbidities (diabetes, hypertension, obesity, cardiovascular disease, chronic lung and kidney ailments, weakened immune system, smoking, cancer, and organ transplant) are more likely to suffer symptoms or progress to serious or fatal conditions (Docherty et al., 2020; Gao et al., 2021; Rashedi et al., 2020 Dec 1; Pollard et al., 2020 Nov 1; Jordan et al., 2020 Mar). Moreover, gender differences, lifestyle habits, viral strains, and amount of exposure to the virus also impact susceptibility to infection and progression to critical illness (Ou et al., 2020 Aug; Ebinger et al., 2020; Zhang et al., 2020; Bousquet et al., 2020; Fricke-Galindo and Falfán-Valencia, 2021). While the established risk factors correlate with disease severity, the risk factors alone do not explain why some young, healthy individuals suffer severe or life-threatening illness. Recent studies demonstrated, the observed variability can be attributed to genetic underliers imparting inter-individual differences in susceptibility to SARS-CoV-2 infection and disease severity (COVID-19., 2021).

Before the COVID-19 outbreak, several studies demonstrated that variations in human genome produce a wide variety of response to infections caused by pathogenic viruses such as influenza, HIV, RSV, HTLV-1, HPV, HBV, HCV, HSV, EPV, parvovirus, norovirus and rotavirus (Kenney et al., 2017). While most studies typically focus on viral genetic determinants of infection severity or host immune response to infection, host genetic influence to viral infections is still relatively less investigated (Asgari and Pousaz, 2021 Dec). The apparent paucity of studies related to host genetics of viral diseases can chiefly be attributed to the outweighing focus on vaccine and antiviral development or investigations on socio-demographic determinants, aimed at expeditious mitigation of viral outbreaks. Notwithstanding the research emphasis directed towards identifying effective prophylactic and therapeutic regimens, studies on host genetic influence on infection susceptibility and severity has recently garnered significant attention. Genetic studies of viral susceptibility and infection severity not only connect genes and genomic loci to infection outcomes, but also contribute to a better understanding of viral pathogenesis and infection mechanisms. Moreover, identification of genetic variants contributing to susceptibility and severity of infections can lead to the development of new antiviral paradigms and offer insights to predict response to therapy and vaccination (Kenney et al., 2017).

In response to the global COVID-19 outbreak, rapid efforts were directed towards unravelling the host genetic contribution to the susceptibility and severity of the disease. Several genome-wide association studies (GWAS) were conducted in ethnically-varied populations, which uncovered potential genomic biomarkers linked to an increased risk of infection and progression to severe clinical manifestations (Severe Covid-19 GWAS Group et al., 2020; Li et al., 2021; Wu et al., 2021; Mousa et al., 2021 Dec; Pairo-Castineira et al., 2021 Mar; Wang et al., 2020 Nov 10; Hu et al., 2021 Feb 3; Horowitz et al., 2021). Parallel to GWAS, which represent an indispensable approach for providing statistical evidence of association with susceptibility loci at genome level, several candidate gene-based, case-control association studies have recently been conducted, interrogating the role of specific gene variants in COVID-19 prognosis. Endorsing the importance of identifying the genetic determinants of SARS-CoV-2 infection, these studies explored within a very short period of time the association between polymorphisms of the candidate genes and susceptibility to infection and variability of disease progression. However, many of the eligible studies reported inconsistent findings and were limited by relatively small sample sizes, warranting a systematic appraisal of the body of knowledge to ascertain the relevance of the candidate gene polymorphisms in COVID-19 susceptibility and severity with greater statistical confidence.

To explore the current knowledge about the genetic influence on susceptibility to SARS-CoV-2 infection and progression to severe disease conditions, we embarked on a systematic literature search of genetic association studies and conducted meta-analyses of all the genetic variants for which, at least three case-control association studies were reported. To the best of our knowledge, this is the first systematic review that summarized all the genetic factors reported to date, which have been evaluated for conferring risk to COVID-19. This study also implemented statistical evaluation of several genetic variants as predictors of clinical phenotypes through meta-analyses of the eligible studies. We believe, the findings of this study will boost our understanding of the host genetic underpinnings of COVID-19 manifestations, and provide information that can be used to identify potential therapeutic targets and devise tailored treatment strategies.

2. Materials and methods

2.1. Strategy for literature search

A literature search of databases including PubMed, Google Scholar, and Embase (for published articles) and bioRxiv (for pre-print articles) was conducted to identify the studies exploring association between various genetic polymorphisms and SARS-CoV-2 infection. Search terms including "SARS-CoV-2" or "COVID-19" and "polymorphism" or "genotype" or "single nucleotide polymorphism (SNP)" and "study" or "case-control association" were used in different combinations to identify the relevant records published till March 15, 2022. Since new reports were published after our initial search and during the course of our study, we extended our search till April 07, 2022, updating our list of studies by including the latest reports and unreferred studies that were previously found. Further, our literature search was supplemented by screening the references listed in all the relevant studies including research articles, meta-analyses, and reviews. After identifying all the relevant studies, the publications were retrieved from the databases and downloaded locally, which was followed by data extraction and synthesis on a worksheet.

2.2. Study identification and selection

The initial review of literature by screening the title and abstract was conducted independently by three reviewers (KG, GK and TP) in an iterative process. The identified records were read carefully, and a second review was performed by the same reviewers and the results were compared and cross-checked. Disagreements on study selection and review process were discussed, and final selection of the studies was made upon reaching consensus by all the three reviewers.

The following eligibility criteria were considered for inclusion of any study for the systematic review and meta-analysis:

1. Article type: case-control association study or cohort study that examined association of genetic variants with SARS-CoV-2 infection susceptibility or severity.
2. Population: patients infected with SARS-CoV-2 and infection was confirmed by RT-PCR or other diagnostic method.
3. Human subjects: study was performed on human subjects only.
4. Genetic information: study that provided genotype information for both cases and controls.
5. Language: study published in English language only.

Studies were rejected if they met one or more of the following exclusion criteria:

1. Studies that reported duplicated findings
2. Animal studies or studies on sibling pairs or family
3. Studies with insufficient data

4. Data from reviews/case reports/abstracts/comments

2.3. Data extraction and quality assessment

Three reviewers (KG, GK and TP) independently screened the records from the initial screening phase, and the eligible studies were examined in-full by two reviewers. A third reviewer independently verified the titles and abstracts. In case of disagreements, all the reviewers discussed the accordance with the inclusion and exclusion criteria to arrive at a consensus. Two reviewers drafted the data synthesis, which was verified by all the reviewers. Publications that were relevant to this study but did not have all the required information were omitted, and raw data were not requested. All the relevant data were extracted according to the above selection criteria and tabulated with the headings: name of the first author and publication year, ethnicity, gene and polymorphism, detection method, and number of cases and control subjects. Allele frequencies, when not provided, were calculated from the genotype frequencies. All the extracted data were carefully evaluated, and the genetic polymorphisms with three or more reported studies were considered for meta-analyses.

2.4. Statistical analysis

To evaluate the strength of association between the genetic polymorphisms and SARS-CoV-2 infection susceptibility and disease severity, the pooled odds ratio (OR) along with 95 % confidence interval (CI) was calculated for six genetic models: allele contrast, homozygote and heterozygote comparisons, and recessive, dominant and over-dominant models. The Mantel–Haenszel and DerSimonian-Liard methods were used to calculate the fixed effects and random effects models, respectively (Robins et al., 1986 Nov 1; Mantel and Haenszel, 1959; DerSimonian and Laird, 1986 Sep 1). Considering the clinical and methodological diversities in the studies, we used the random effects model to report the pooled ORs in this study as this model incorporates the inter-study variability, providing wider CIs (Whitehead, 2002). To assess the inter-study heterogeneity, we used Cochran's χ^2-based Q test and I^2 metric. Q is distributed as a χ^2 statistic with $r - 1$ (r = number of studies) degrees of freedom (df) (Cochran, 1954 Mar). Heterogeneity was quantified using the I^2 metric (I^2 = (Q - df) / Q), which falls within the range 0–100 %. The degree of heterogeneity is indicated by the I^2 values: no heterogeneity (I^2 = 0–25 %), moderate heterogeneity (I^2 = 25–50 %), large heterogeneity (I^2 = 50–75 %), and extreme heterogeneity (I^2 = 75–100 %) (Higgins et al., 2003 Sep 4). If $P < 0.10$, the heterogeneity was considered statistically significant (Higgins and Thompson, 2002 Jun 15). Control groups of the included studies were examined for Hardy-Weinberg equilibrium (Zintzaras et al., 2005 Jun). Publication bias was assessed by Egger's linear regression analysis test for funnel plot asymmetry (Egger et al., 1997 Sep 13; Ioannidis et al., 2003 Feb 15) and Kendall's tau-based Begg-Mazumdar test (Begg and Mazumdar, 1994). Meta-analyses were performed stratifying the data on the basis of susceptibility to SARS-CoV-2 infection and COVID-19 severity. Meta-analyses results were graphically represented as forest plots. In the forest plot, the solid black square and diamond represent individual effect estimates and pooled estimates, respectively. The size of the solid black square indicates the DerSimonian-Laird weights of the corresponding studies, and the horizontal line passing through the diamond/square represents the CIs. Statistical analyses were carried out with StatsDirect software (version 3.3.4). Two-sided P value with $P < 0.05$ was considered statistically significant.

3. Results

3.1. Systematic search for potential studies

Systematic literature search in PubMed, Google Scholar and Embase (for published articles), and bioRxiv (for pre-print articles) till April 07, 2022, provided 631 relevant records. After evaluation of the records by titles and abstracts, 547 studies were excluded as they did not match the inclusion criteria. Altogether, 84 studies were identified, which examined the association of 130 polymorphisms in 61 genes with COVID-19 (Table 1). The extracted data included: name of the first author and year of publication, gene name, polymorphism, study population, SARS-CoV-2 detection method, number of cases and controls, information about association, and reference. Among the 130 polymorphisms, the polymorphisms that were examined in $\geq$ 3 studies were identified and considered for meta-analyses. A total of 49 studies were finally included in the meta-analyses. The included studies were segregated on the basis of data provided for susceptibility to SARS-CoV-2 infection and COVID-19 severity: 31 studies for susceptibility and 37 studies for severity. Among them, 18 studies provided data for both susceptibility and severity. In the analysis for susceptibility, confirmed COVID-19 cases were compared with uninfected control subjects. In the analysis for severity, patients were considered to have severe COVID-19 if they were critically ill and hospitalized/admitted to ICU/died. Non-severe group comprised of the COVID-19-positive individuals who were asymptomatic/mildly symptomatic/hospitalized but did not require ICU care. The search strategy and selection of studies in this systematic review and meta-analysis were based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and summarized in Fig. 1.

3.2. Summary statistics

A total of 11 genes (*ACE1, ACE2, AGTR1, APOE, CCR5, IFITM3, IFNL3/4, IFNL4, TMPRSS2, TNFA*, and *VDR*) with 7 and 11 polymorphisms tested for association with susceptibility to SARS-CoV-2 infection and severe COVID-19, respectively, were included in this meta-analysis. The genotype distribution and allele frequency of the studies on susceptibility and severity are summarized in Table 2 and Table 3, respectively. The studies for susceptibility analysis included: *ACE1* I/D rs4646994/rs1799752 (Annunziata et al., 2021 Aug 20; Gong et al., 2021; Aladag et al., 2021 Sep; Papadopoulou et al., 2022 Mar; Akbari et al., 2022 Feb; Calabrese et al., 2021 Jan; Saad et al., 2021 Dec; Möhlendick et al., 2021 Oct 1; Gómez et al., 2020 Dec; Hubacek et al., 2021 Aug; Kouhpayeh et al., 2021 Nov 17; Mahmood et al., 2022 Feb; Mir et al., 2021 Oct 27); *ACE2* rs2285666 (Möhlendick et al., 2021 Oct 1; Alimoradi et al., 2022 Mar 19; Gómez et al., 2020 Dec; Mahmood et al., 2022 Feb); *APOE* rs429358 (Kuo et al., 2020 May 26; Al-Jaf et al., 2021 Nov; Hilser et al., 2021 Jan); *CCR5* rs333 (Bernas et al., 2021; Cuesta-Llavona et al., 2021; Hubacek et al., 2021; Gómez et al., 2020); *IFITM3* rs12252 (Cuesta-Llavona et al., 2021; Gómez et al., 2021; Schönfelder et al., 2021); *TMPRSS2* rs12329760 (Ravikanth et al., 2021; Rokni et al., 2022; Schönfelder et al., 2021; Andolfo et al., 2021), and *TNFA* rs1800629 (Ali et al., 2022; Heidari Nia et al., 2022; Saleh et al., 2020). Severity-wise analysis was performed for *ACE1* I/D rs4646994/rs1799752 (Karakaş Çelik et al., 2021 Oct; Gong et al., 2021; Gunal et al., 2021 Jun; Martínez-Gómez et al., 2022 Feb; Baştuğ et al., 2021 Dec 8; Akbari et al., 2022 Feb; Saad et al., 2021 Dec; Möhlendick et al., 2021 Oct 1; Cafiero et al., 2021 May; Gómez et al., 2020 Dec; Hubacek et al., 2021 Aug; Kouhpayeh et al., 2021 Nov 17; Mahmood et al., 2022 Feb; Mir et al., 2021 Oct 27; Verma et al., 2021 Jul; Sabater Molina et al., 2022); *ACE2* rs2285666 (Karakaş Çelik et al., 2021 Oct; Martínez-Gómez et al., 2022 Feb; Möhlendick et al., 2021 Oct 1; Alimoradi et al., 2022 Mar 19; Gómez et al., 2020 Dec; Mahmood et al., 2022 Feb; Sabater Molina et al., 2022); *ACE2* rs2106809 (Karakaş Çelik et al., 2021 Oct; Cafiero et al., 2021 May; Sabater Molina et al., 2022); *ACE2* rs2074192 (Martínez-Gómez et al., 2022 Feb; Cafiero et al., 2021 May; Sabater Molina et al., 2022; Wang et al., 2022 Jan); *AGTR1* rs5186 (Cafiero et al., 2021 May; Kouhpayeh et al., 2021 Nov 17; Sabater Molina et al., 2022); *IFITM3* rs12252 (Alghamdi et al., 2021; Cuesta-Llavona et al., 2021; Gómez et al., 2021; Schönfelder et al., 2021; Zhang et al., 2020); *IFNL3/4* rs12979860 (Agwa et al., 2021; Amodio

Table 1
Characteristics of the studies reporting gene polymorphisms related to SARS-CoV-2 infection.

Author, year	Gene	Polymorphism	Population	Detection method	Case	Control	Association Yes/No	Reference
Annunziata, 2021	*ACE1*	I/D	Italy	RT-PCR	20	19	Yes	(Annunziata et al., 2021 Aug 20)
Çelik, 2021	*ACE1*	I/D	Turkey	RFLP-PCR	154	NA	No	(Karakaş Çelik et al., 2021 Oct)
Gong, 2022	*ACE*	I/D	China	PCR	421	441	Yes	(Gong et al., 2021)
Gunal, 2021	*ACE*	I/D	Turkey	PCR	90	NA	Yes	(Gunal et al., 2021 Jun)
Martínez-Gómez, 2022	*ACE*	I/D	Mexico	RT-PCR	481	NA	No	(Martínez-Gómez et al., 2022 Feb)
Aladag, 2021	*ACE1*	I/D	Turkey	PCR	112	298	Yes	(Aladag et al., 2021 Sep)
Papadopoulou,2021	*ACE1*	I/D	Greece	PCR	73	316	Yes	(Papadopoulou et al., 2022 Mar)
Serdal Baştuğ, 2022	*ACE1*	I/D	Turkey	PCR	100	NA	No	(Baştuğ et al., 2021 Dec 8)
Akbari, 2022	*ACE1*	rs1799752	Iran	ARMS-PCR	91	91	Yes	(Akbari et al., 2022 Feb)
Calabrese, 2021	*ACE1*	rs1799752	Italy	NA	68	222	Yes	(Calabrese et al., 2021 Jan)
Saad, 2021	*ACE1*	rs1799752	Lebanon	PCR	232	155	Yes	(Saad et al., 2021 Dec)
Möhlendick, 2021	*ACE1*	rs1799752	Germany	PCR	297	253	No	(Möhlendick et al., 2021 Oct 1)
Cafiero, 2021	*ACE1*	rs1799752	Italy	Commercial kit	104	NA	Yes	(Cafiero et al., 2021 May)
Iñiguez, 2021	*ACE1*	rs4341	Spain	RT-PCR	128	NA	Yes	(Íñiguez et al., 2021 Aug)
Iñiguez, 2021	*ACE1*	rs4343	Spain	RT-PCR	128	NA	Yes	(Íñiguez et al., 2021 Aug)
Alimoradi, 2022	*ACE1*	rs4343	Iran	RFLP-PCR	79	50	Yes	(Alimoradi et al., 2022 Mar 19)
Martínez-Gómez, 2022	*ACE1*	rs4344	Mexico	RT-PCR	481	NA	No	(Martínez-Gómez et al., 2022 Feb)
Akbari, 2022	*ACE1*	rs4359	Iran	ARMS-PCR	91	91	Yes	(Akbari et al., 2022 Feb)
Gómez, 2020	*ACE1*	rs4646994	Spain	RFLP-PCR	204	536	Yes	(Gómez et al., 2020 Dec)
Hubacek, 2021	*ACE1*	rs4646994	Czech Republic	PCR	408	2579	Yes	(Hubacek et al., 2021 Aug)
Kouhpayeh, 2021	*ACE1*	rs4646994	Iran	PCR	258	244	Yes	(Kouhpayeh et al., 2021 Nov 17)
Mahmood, 2022	*ACE1*	rs4646994	Iraq	PCR	99	96	No	(Mahmood et al., 2022 Feb)
Mir, 2021	*ACE1*	rs4646994	Saudi Arabia	ARMS PCR	117	150	Yes	(Mir et al., 2021 Oct 27)
Verma, 2021	*ACE1*	rs4646994	India	PCR-AFLP	269	NA	Yes	(Verma et al., 2021 Jul)
Molina, 2022	*ACE1*	rs4646994	Spain	PCR	309	NA	Yes	(Sabater Molina et al., 2022)
Çelik, 2021	*ACE2*	rs2106809	Turkey	RFLP-PCR	77	NA	No	(Karakaş Çelik et al., 2021 Oct)
Molina, 2022	*ACE2*	rs2106809	Spain	PCR	309	NA	Yes	(Sabater Molina et al., 2022)
Cafiero, 2021	*ACE2*	rs2106809	Italy	Commercial kit	104	NA	No	(Cafiero et al., 2021 May)
Molina, 2022	*ACE2*	rs2106809	Spanish	PCR	309	NA	Yes	(Sabater Molina et al., 2022)
Molina, 2022	*ACE2*	rs1978124	Spain	PCR	309	NA	Yes	(Sabater Molina et al., 2022)
Wang, 2022	*ACE2*	rs20248683	China	TaqMan-PCR	191	NA	No	(Wang et al., 2022 Jan)
Cafiero, 2021	*ACE2*	rs2074192	Italy	Commercial kit	104	NA	Yes	(Cafiero et al., 2021 May)
Wang, 2022	*ACE2*	rs2074192	China	TaqMan-PCR	191	NA	No	(Wang et al., 2022 Jan)
Molina, 2022	*ACE2*	rs2074192	Spain	PCR	309	NA	Yes	(Sabater Molina et al., 2022)
Martínez-Gómez, 2022	*ACE2*	rs2074192	Mexico	RT-PCR	481	NA	No	(Martínez-Gómez et al., 2022 Feb)
Traets, 2022	*ACE2*	rs2285666	Europe	RT-PCR	116	NA	No	(Traets et al., 2022 Jan 7)
Mahmood, 2022	*ACE2*	rs2285666	Iraq	PCR	99	96	No	(Mahmood et al., 2022 Feb)
Gómez, 2020	*ACE2*	rs2285666	Spain	RFLP-PCR	204	536	No	(Gómez et al., 2020 Dec)
Möhlendick, 2021	*ACE2*	rs2285666	Germany	PCR	297	253	Yes	(Möhlendick et al., 2021 Oct 1)
Molina, 2022	*ACE2*	rs2285666	Spain	PCR	88	NA	Yes	(Sabater Molina et al., 2022)
Çelik, 2021	*ACE2*	rs2285666	Turkey	RFLP-PCR	77	NA	No	(Karakaş Çelik et al., 2021 Oct)
Alimoradi, 2022	*ACE2*	rs2285666	Iran	RFLP-PCR	79	50	Yes	(Alimoradi et al., 2022 Mar 19)
Martínez-Gómez, 2022	*ACE2*	rs2285666	Mexico	RT-PCR	481	NA	Yes	(Martínez-Gómez et al., 2022 Feb)
Mir, 2021	*ACE2*	rs4240157	Saudi Arabia	ARMS PCR	117	100	Yes	(Mir et al., 2021 Oct 27)
Wang, 2022	*ACE2*	rs4240157	China	TaqMan-PCR	194	NA	No	(Wang et al., 2022 Jan)
Wang, 2022	*ACE2*	rs4646142	China	TaqMan-PCR	180	NA	No	(Wang et al., 2022 Jan)
Djukic, 2022	*ACE2*	rs4646116	Serbia	TaqMan PCR	255	236	No	(Djukic et al., 2022 Mar 14)
Wang, 2022	*ACE2*	rs6632677	China	TaqMan-PCR	196	NA	Yes	(Wang et al., 2022 Jan)
Cafiero, 2021	*AGT*	rs4762	Italy	Commercial kit	104	NA	No	(Cafiero et al., 2021 May)
Cafiero, 2021	*AGT*	rs699	Italy	Commercial kit	104	NA	Yes	(Cafiero et al., 2021 May)
Kouhpayeh, 2021	*AGT*	rs699	Iran	RFLP-PCR	217	245	Yes	(Kouhpayeh et al., 2021 Nov 17)
Molina, 2022	*AGTR1*	rs5183	Spain	PCR	309	NA	Yes	(Sabater Molina et al., 2022)
Molina, 2022	*AGTR1*	rs5185	Spain	PCR	309	NA	No	(Sabater Molina et al., 2022)
Cafiero, 2021	*AGTR1*	rs5186	Italy	Commercial kit	104	NA	No	(Cafiero et al., 2021 May)
Molina, 2022	*AGTR1*	rs5186	Spain	PCR	309	NA	No	(Sabater Molina et al., 2022)
Kouhpayeh, 2021	*AGTR1*	rs5186	Iran	RFLP-PCR	207	244	No	(Kouhpayeh et al., 2021 Nov 17)

(*continued on next page*)

Table 1 (*continued*)

Author, year	Gene	Polymorphism	Population	Detection method	Case	Control	Association Yes/No	Reference
Izmailova, 2022	*AGTR1*	rs5186	Ukraine	RFLP-PCR	294	82	Yes	(Izmailova et al., 2022 Mar)
Kuo, 2020	*APOE*	rs429358	England	NA	622	322,326	Yes	(Kuo et al., 2020 May 26)
Al-Jaf, 2021	*APOE*	rs429358	Iraq	PCR	105	114	Yes	(Al-Jaf et al., 2021 Nov)
Hilser, 2021	*APOE*	rs429358	England	NA	719	1438	Yes	(Hilser et al., 2021 Jan)
del Ser, 2021	*APOE*	rs429358	Spain	NA	913	NA	Yes	(del Ser et al., 2021 Jan)
Hubacek, 2021	*APOE*	rs429358	Czech Republic	TaqMan-PCR	408	2606	Yes	(Hubacek et al., 2021)
Lehrer and Rheinstein, 2021	*BIN1*	rs744373	Europe	NA	619	NA	Yes	(Lehrer and Rheinstein ph., 2021;3(2):13.)
Cantalupo, 2021	*CCR5*	rs35951367	Italy	TaqMan PCR	202	929	Yes	(Cantalupo et al., 2021 May 20)
Cantalupo, 2021	*CCR5*	rs34418657	Italy	TaqMan PCR	221	1084	Yes	(Cantalupo et al., 2021 May 20)
Cuesta-Llavona, 2021	*CCR5*	rs333	Spain	PCR	801	650	Yes	(Cuesta-Llavona et al., 2021 Sep)
Bernas, 2021	*CCR5*	rs333	Germany	NA	5536	105,008	No	(Bernas et al., 2021 Apr)
Gómez, 2020	*CCR5*	rs333	Spain	PCR	294	460	Yes	(Gómez et al., 2020)
Hubacek, 2021	*CCR5*	rs333	Czech Republic	PCR	416	2404	Yes	(Hubacek et al., 2021 Mar 17)
Al-Anouti, 2021	*CYP2R1*	rs10500804	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Kotur, 2021	*CYP2R1*	rs10741657	Serbia	TaqMan PCR	120	NA	Yes	(Kotur et al., 2021 Jun)
Al-Anouti, 2021	*CYP2R1*	rs11023373	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*CYP2R1*	rs11023374	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*CYP2R1*	rs1993116	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*CYP2R1*	rs7935792	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Agwa, 2021	*DDR1*	rs4618569	Egypt	TaqMan PCR	141	100	Yes	(Agwa et al., 2021 May 28)
de Lima Beltrão, 2022	*DIO2*	rs225014	Brazil	TaqMan PCR	220	NA	Yes	(de Lima Beltrão et al., 2022 May 17)
Kotur, 2021	*DMGDH*	rs17823744	Serbia	TaqMan PCR	120	NA	No	(Kotur et al., 2021 Jun)
Posadas-Sánchez, 2021	*DPP4*	rs3788979	Mexico	RT-PCR	104	256	Yes	(Posadas-Sánchez et al., 2021 Jul)
Annunziata, 2021	*Factor V*	H2R	Italy	RT-PCR	20	19	No	(Annunziata et al., 2021 Aug 20)
Annunziata, 2021	*Factor V*	Leiden	Italy	RT-PCR	20	19	Yes	(Annunziata et al., 2021 Aug 20)
Traets, 2022	*Factor X*	rs3211783	Europe	RT-PCR	116	NA	No	(Traets et al., 2022 Jan 7)
López-Martínez, 2022	*FCGR2A*	rs1801274	Spain	Taqman PCR	453	NA	Yes	(López-Martínez et al., 2022 Mar)
López-Martínez, 2022	*FCGR3A*	rs396991	Spain	Taqman PCR	453	NA	No	(López-Martínez et al., 2022 Mar)
Petrazzuolo, 2020	*FPR1*	rs867228	France	Fluorescently labelled probes	140	NA	No	(Petrazzuolo A)
Petrazzuolo, 2020	*FPR1*	rs5030880	France	Fluorescently labelled probes	140	NA	No	(Petrazzuolo A)
Coto, 2022	*Furin*	rs4702	Spain	Taqman PCR	428	NA	Yes	(Coto et al., 2022 Aug)
Coto, 2022	*Furin*	rs6224	Spain	Taqman PCR	428	NA	Yes	(Coto et al., 2022 Aug)
Nishida, 2022	*FUT2*	rs1047781	Japan	NA	461	1193	Yes	(Nishida et al., 2022 Dec)
Al-Anouti, 2021	*GC*	rs113574864	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*GC*	rs113876500	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*GC*	rs182901986	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Kotur, 2021	*GC*	rs2282679	Serbia	TaqMan PCR	119	NA	No	(Kotur et al., 2021 Jun)
Al-Anouti, 2021	*GC*	rs59241277	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*GC*	rs60349934	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Jerotic,2022	*GPX1*	rs1050450	Serbia	RT-PCR	229	229	Yes	(Jerotic D)
Coric, 2021	*GSTA1*	rs3957357	Serbia	RFLP-PCR	207	230	No	(Coric et al., 2021 Dec)
Coric, 2021	*GSTM1*	Active/ null	Serbia	Multiplex PCR	207	231	No	(Coric et al., 2021 Dec)
Abbas, 2021	*GSTM1*	Active/ null	India	Multiplex PCR	269	NA	Yes	(Abbas et al., 2021 Jun 12)
Coric, 2021	*GSTM3*	rs1332018	Serbia	RT-PCR	188	191	Yes	(Coric et al., 2021 Dec)
Djukic, 2022	*GSTO1*	rs4925	Serbia	TaqMan PCR	255	236	Yes	(Djukic et al., 2022 Mar 14)
Djukic, 2022	*GSTO2*	rs156697	Serbia	TaqMan PCR	255	236	Yes	(Djukic et al., 2022 Mar 14)
Coric, 2021	*GSTP1*	rs1138272	Serbia	RT-PCR	206	220	Yes	(Coric et al., 2021; Jerotic D)
Coric, 2021	*GSTP1*	rs1695	Serbia	RT-PCR	196	229	Yes	(Coric et al., 2021 Dec)
Coric, 2021	*GSTT1*	Active/ null	Serbia	Multiplex PCR	207	231	No	(Coric et al., 2021 Dec)
Abbas, 2021	*GSTT1*	Active/ null	India	Multiplex PCR	269	NA	Yes	(Abbas et al., 2021 Jun 12)
Schönfelder, 2021	*IFITM3*	rs12252	Germany	PCR	239	253	No	(Schönfelder et al., 2021 Jun)

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Table 1 (*continued*)

Author, year	Gene	Polymorphism	Population	Detection method	Case	Control	Association Yes/No	Reference
Gómez, 2021	*IFITM3*	rs12252	Spain	RT-PCR	311	440	Yes	(Gómez et al., 2021 Jan)
Cuesta-Llavona, 2021	*IFITM3*	rs12252	Spain	RT-PCR	484	182	Yes	(Cuesta-Llavona et al., 2021)
Zhang, 2020	*IFITM3*	rs12252	China	PCR	83	NA	Yes	(Zhang et al., 2020 Jul 1)
Alghamdi, 2021	*IFITM3*	rs12252	Saudi Arabia	RT-PCR	861	NA	Yes	(Alghamdi et al., 2021 Jul)
Cuesta-Llavona, 2021	*IFITM3*	rs34481144	Spain	RT-PCR	484	182	Yes	(Cuesta-Llavona et al., 2021)
Schönfelder, 2021	*IFITM3*	rs34481144	Germany	PCR	239	253	No	(Schönfelder et al., 2021 Jun)
Rahimi, 2021	*IFNL3/4*	rs12979860	Iran	RFLP-PCR	750	NA	Yes	(Rahimi et al., 2021 Dec)
Agwa, 2021	*IFNL3/4*	rs12979860	Egypt	TaqMan PCR	141	100	Yes	(Agwa et al., 2021 May 28)
Amodio, 2020	*IFNL3/4*	rs12979860	Italy	Taqman PCR	381	NA	Yes	(Amodio et al., 2020 Oct 15)
Grimaudo, 2021	*IFNL3/4*	rs12979860	Italy	RT-PCR	383	NA	No	(Grimaudo et al., 2021 Jun)
Rahimi, 2021	*IFNL3*	rs12980275	Iran	RFLP-PCR	750	NA	Yes	(Rahimi et al., 2021 Dec)
Rahimi, 2021	*IFNL3*	rs8099917	Iran	RFLP-PCR	750	NA	Yes	(Rahimi et al., 2021 Dec)
Grimaudo, 2021	*IFNL4*	rs368234815	Italy	RT-PCR	301	NA	No	(Grimaudo et al., 2021 Jun)
Amodio, 2020	*IFNL4*	rs368234815	Italy	Taqman PCR	300	NA	Yes	(Amodio et al., 2020 Oct 15)
Rahimi, 2021	*IFNL4*	rs368234815	Iran	RFLP-PCR	750	NA	Yes	(Rahimi et al., 2021 Dec)
Avendaño-Félix, 2021	*IL-10*	rs1800871	Mexico	RT-PCR	193	NA	No	(Avendaño-Félix et al., 2021 Oct 1)
Avendaño-Félix, 2021	*IL-10*	rs1800872	Mexico	RT-PCR	193	NA	No	(Avendaño-Félix et al., 2021 Oct 1)
Azevedo, 2021	*IL17A*	rs3819025	Brazil	RT-PCR	19	10	Yes	(Azevedo et al., 2021 Mar)
Azevedo, 2021	*IL17A*	rs2275913	Brazil	RT-PCR	20	9	No	(Azevedo et al., 2021 Mar)
Ahmed and Ad'hiah, 2022	*IL37*	rs2466449	Iraq	PCR	100	100	No	(Ahmed and Ad'hiah, 2022 Feb)
Ahmed and Ad'hiah, 2022	*IL37*	rs3811042	Iraq	PCR	100	100	No	(Ahmed and Ad'hiah, 2022 Feb)
Ahmed and Ad'hiah, 2022	*IL37*	rs3811043	Iraq	PCR	100	100	No	(Ahmed and Ad'hiah, 2022 Feb)
Ahmed and Ad'hiah, 2022	*IL37*	rs3811045	Iraq	PCR	100	100	No	(Ahmed and Ad'hiah, 2022 Feb)
Ahmed and Ad'hiah, 2022	*IL37*	rs3811046	Iraq	PCR	100	100	Yes	(Ahmed and Ad'hiah, 2022 Feb)
Ahmed and Ad'hiah, 2022	*IL37*	rs3811047	Iraq	PCR	100	100	Yes	(Ahmed and Ad'hiah, 2022 Feb)
Chen, 2021	*IL6*	rs1800796	China	PCR	105	149	Yes	(Chen T)
Chen, 2021	*IL6*	rs1524107	China	PCR	105	149	Yes	(Chen T)
Fishchuk, 2021	*IL6*	rs1800795	Ukraine	PCR	31	NA	Yes	(Fishchuk et al., 2021 Dec 6)
Gómez, 2020	*LZTFL1*	rs67959919	Spain	RFLP-PCR	294	460	Yes	(Gómez et al., 2020)
Medetalibeyoglu, 2021	*MBL*	rs1800450	Turkey	RFLP-PCR	284	100	Yes	(Medetalibeyoglu et al., 2021 Apr)
Speletas, 2021	*MBL*	rs1800450	Europe	RFLP-PCR	264	NA	Yes	(Speletas et al., 2021 Nov)
Grimaudo, 2021	*MERTK*	rs4374383	Italy	RT-PCR	291	NA	No	(Grimaudo et al., 2021 Jun)
Annunziata, 2021	*MTHFR*	A1298C	Italy	RT-PCR	20	19	No	(Annunziata et al., 2021 Aug 20)
Annunziata, 2021	*MTHFR*	C677T	Italy	RT-PCR	20	19	No	(Annunziata et al., 2021 Aug 20)
van Moorsel, 2021	*MUC5B*	rs35705950	Netherlands	RT-PCR	83	611	Yes	(van Moorsel et al., 2021 Nov)
Al-Anouti, 2021	*NADSYN1*	rs10898210	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Kotur, 2021	*NADSYN1*	rs12785878	Serbia	TaqMan PCR	120	NA	Yes	(Kotur et al., 2021 Jun)
Al-Anouti, 2021	*NADSYN1*	rs4944076	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*NADSYN1*	rs4944979	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*NADSYN1*	rs4944997	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*NADSYN1*	rs4944998	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Maes, 2021	*NLPR3*	rs10157379	Brazil	TaqMan qPCR	528	NA	Yes	(Maes et al., 2022 Jan)
Maes, 2021	*NLPR3*	rs10754558	Brazil	TaqMan qPCR	528	NA	Yes	(Maes et al., 2022 Jan)
Annunziata, 2021	*PAI-1*	−675 I/D, 4G/5G	Italy	RT-PCR	20	19	Yes	(Annunziata et al., 2021 Aug 20)
Yesil Sayin, 2021	*PER3*	rs57875989	Turkey	PCR	200	100	Yes	(Yesil Sayin et al., 2021)
Grimaudo, 2021	*PNPLA3*	rs738409	Italy	RT-PCR	298	NA	Yes	(Grimaudo et al., 2021 Jun)
Kotur, 2021	*PPCDC*	rs2120019	Serbia	TaqMan PCR	120	NA	No	(Kotur et al., 2021 Jun)
Kerget, 2021	*PTX3*	rs2305619	Turkey	STA-PCR	94	NA	No	(Kerget et al., 2021 Jul 31)
Kerget, 2021	*PTX3*	rs1840680	Turkey	STA-PCR	94	NA	Yes	(Kerget et al., 2021 Jul 31)
El-Hefnawy, 2022	*SERPINA4*	rs2093266	Egypt	TaqMan RT-PCR	146	81	Yes	(El-Hefnawy et al., 2022 Mar)
El-Hefnawy, 2022	*SERPINA5*	rs1955656	Egypt	TaqMan RT-PCR	146	81	Yes	(El-Hefnawy et al., 2022 Mar)
Jerotic,2022	*SOD2*	rs4880	Serbia	RT-PCR	229	229	Yes	(Jerotic D)
Traets, 2022	*TIRAP*	rs8177374	Europe	RT-PCR	116	NA	Yes	(Traets et al., 2022 Jan 7)
Grimaudo, 2021	*TLL1*	rs17047200	Italy	RT-PCR	371	NA	Yes	(Grimaudo et al., 2021 Jun)
Agwa, 2021	*TLL1*	rs17047200	Egypt	TaqMan PCR	141	100	Yes	(Agwa et al., 2021 May 28)
Alseoudy, 2022	*TLR3*	rs3775290	Egypt	TaqMan RT-PCR	136	100	No	(Alseoudy et al., 2022 Feb)
Croci, 2021	*TLR3*	L412F	Italy	RT-PCR	338	300	Yes	(Croci et al., 2021 Dec)
Taha, 2021	*TLR4*	rs4986790	Egypt	RFLP-PCR	300	NA	Yes	(Taha et al., 2022 Mar 1)

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Table 1 (*continued*)

Author, year	Gene	Polymorphism	Population	Detection method	Case	Control	Association Yes/No	Reference
Taha, 2022	*TLR4*	rs4986790	Egypt	RFLP-PCR	145	NA	Yes	(Taha et al., 2021 Nov)
Taha, 2021	*TLR4*	rs4986791	Egypt	RFLP-PCR	300	NA	Yes	(Taha et al., 2022 Mar 1)
Alseoudy, 2022	*TLR7*	rs179008	Egypt	TaqMan RT-PCR	136	100	No	(Alseoudy et al., 2022 Feb)
Andolfo, 2021	*TMPRSS2*	rs12329760	Italy	TaqMan RT-PCR	996	3763	Yes	(Andolfo et al., 2021)
Schönfelder, 2021	*TMPRSS2*	rs12329760	German	RFLP-PCR	239	253	No	(Schönfelder et al., 2021 Apr)
Ravikanth, 2021	*TMPRSS2*	rs12329760	India	PCR	510	500	Yes	(Ravikanth et al., 2021 Sep)
Wulandari, 2021	*TMPRSS2*	rs12329760	Indonesia	Taqman PCR	95	NA	Yes	(Wulandari et al., 2021)
Rokni, 2022	*TMPRSS2*	rs12329760	Iran	ARMS-PCR, RFLP-PCR	288	288	Yes	(Rokni et al., 2022 Apr)
Schönfelder, 2021	*TMPRSS2*	rs2070788	German	RFLP-PCR	239	253	No	(Schönfelder et al., 2021 Apr)
Schönfelder, 2021	*TMPRSS2*	rs383510	German	RFLP-PCR	239	253	Yes	(Schönfelder et al., 2021 Apr)
Rokni, 2022	*TMPRSS2*	rs17854725	Iran	ARMS-PCR, RFLP-PCR	288	288	Yes	(Rokni et al., 2022 Apr)
Rokni, 2022	*TMPRSS2*	rs75603675	Iran	ARMS-PCR, RFLP-PCR	288	288	No	(Rokni et al., 2022 Apr)
Saleh, 2020	*TNFA*	G308A	Egypt	RT-PCR	900	184	Yes	(Saleh et al., 2020 Nov)
Heidari Nia, 2021	*TNFA*	rs1800629	Iran	ARMS-PCR	275	275	Yes	(Heidari Nia et al., 2022)
Ali, 2022	*TNFA*	G308A	Kurdistan	PCR	125	114	Yes	(Ali et al., 2022 May)
Fishchuk, 2021	*TNFA*	rs1800629	Ukraine	PCR	31	NA	Yes	(Fishchuk et al., 2021 Dec 6)
Heidari Nia, 2021	*TNFB*	rs909253	Iran	ARMS-PCR	275	275	Yes	(Heidari Nia et al., 2022)
Russo, 2021	*TNFRSF13C*	rs61756766	Italy	TaqMan PCR	500	NA	Yes	(Russo et al., 2021 Jun 8)
Al-Anouti, 2021	*VDR*	rs10875694	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Abdollahzadeh, 2021	*VDR*	rs11568820	Iran	RFLP PCR	500	NA	Yes	(Abdollahzadeh et al., 2021 Dec)
Al-Anouti, 2021	*VDR*	rs11574018	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*VDR*	rs11574024	Dubai	Infinium Global Screening Array	646	NA	Yes	(Al-Anouti et al., 2021 Oct 20)
Al-Anouti, 2021	*VDR*	rs116886958	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Apaydin, 2021	*VDR*	rs1544410	Turkey	RFLP-PCR	267	55	No	(Apaydin et al., 2022 Jun)
Abdollahzadeh, 2021	*VDR*	rs1544410	Iran	RFLP-PCR	500	NA	Yes	(Abdollahzadeh et al., 2021 Dec)
Fishchuk, 2021	*VDR*	rs1544410	Ukraine	PCR	31	NA	Yes	(Fishchuk et al., 2021 Dec 6)
Apaydin, 2021	*VDR*	rs2228570	Turkey	RFLP-PCR	268	150	Yes	(Apaydin et al., 2022 Jun)
Abdollahzadeh, 2021	*VDR*	rs2228570	Iran	RFLP-PCR	500	NA	Yes	(Abdollahzadeh et al., 2021 Dec)
Kotur, 2021	*VDR*	rs2228570	Serbia	TaqMan PCR	120	NA	No	(Kotur et al., 2021 Jun)
Al-Anouti, 2021	*VDR*	rs2239181	Dubai	Infinium Global Screening Array	646	NA	No	(Al-Anouti et al., 2021 Oct 20)
Abdollahzadeh, 2021	*VDR*	rs4516035	Iran	RFLP-PCR	500	NA	Yes	(Abdollahzadeh et al., 2021 Dec)
Apaydin, 2021	*VDR*	rs731236	Turkey	RFLP-PCR	267	150	Yes	(Apaydin et al., 2022 Jun)
Abdollahzadeh, 2021	*VDR*	rs731236	Iran	RFLP-PCR	500	NA	No	(Abdollahzadeh et al., 2021 Dec)
Fishchuk, 2021	*VDR*	rs731236	Ukraine	PCR	31	NA	Yes	(Fishchuk et al., 2021 Dec 6)
Abdollahzadeh, 2021	*VDR*	rs739837	Iran	RFLP-PCR	500	NA	No	(Abdollahzadeh et al., 2021 Dec)
Abdollahzadeh, 2021	*VDR*	rs757343	Iran	RFLP-PCR	500	NA	Yes	(Abdollahzadeh et al., 2021 Dec)
Apaydin, 2021	*VDR*	rs7975232	Turkey	RFLP-PCR	273	150	Yes	(Apaydin et al., 2022 Jun)
Abdollahzadeh, 2021	*VDR*	rs7975232	Iran	RFLP-PCR	500	NA	Yes	(Abdollahzadeh et al., 2021 Dec)

PCR, polymerase chain reaction; RT-PCR, Real time PCR; ARMS, amplification refractory mutation system; RFLP, restriction fragment length polymorphism; STA, specific target amplification; NA, not available.

et al., 2020; Grimaudo et al., 2021; Rahimi et al., 2021); *IFNL4* rs368234815 (Amodio et al., 2020; Grimaudo et al., 2021; Rahimi et al., 2021); *TMPRSS2* rs12329760 (Ravikanth et al., 2021; Rokni et al., 2022; Schönfelder et al., 2021; Wulandari et al., 2021); *TNFA* rs1800629 (Ali et al., 2022; Fishchuk et al., 2021; Heidari Nia et al., 2022; Saleh et al., 2020), and *VDR* rs731236 (Abdollahzadeh et al., 2021; Apaydin et al., 2022; Fishchuk et al., 2021). Among the studies included in the susceptibility analysis, the control groups of the following studies did not follow Hardy-Weinberg equilibrium (HWE): *ACE1* I/D rs4646994/rs1799752 (Aladag et al., 2021 Sep; Mir et al., 2021 Oct 27); *ACE2* rs2285666 (Möhlendick et al., 2021 Oct 1); *CCR5* rs333 (Hubacek et al., 2021 Mar 17); *TMPRSS2* rs12329760 (Andolfo et al., 2021) and *TNFA* rs1800629 (Ali et al., 2022; Saleh et al., 2020). In the severity analysis, HWE did not exist in the control groups of the following studies: *ACE1* I/D rs4646994/rs1799752 (Gong et al., 2021; Gunal et al., 2021 Jun; Akbari et al., 2022 Feb; Möhlendick et al., 2021 Oct 1; Kouhpayeh et al., 2021 Nov 17); *ACE2* rs2285666 (Martínez-Gómez et al., 2022 Feb; Möhlendick et al., 2021 Oct 1); *ACE2* rs2106809 (Cafiero et al., 2021 May; Sabater Molina et al., 2022); *ACE2* rs2074192 (Martínez-Gómez et al., 2022 Feb; Sabater Molina et al., 2022; Wang et al., 2022 Jan), *IFITM3* rs12252 (Schönfelder et al., 2021 Jun); *TMPRSS2* rs12329760 (Wulandari et al., 2021); *TNFA* rs1800629 (Saleh et al., 2020 Nov) and *VDR* rs731236 (Abdollahzadeh et al., 2021; Apaydin et al., 2022).

3.3. Quantitative synthesis

3.3.1. Meta-analyses of genetic variants with susceptibility to SARS-CoV-2 infection

Seven genetic polymorphisms (*ACE1* I/D rs4646994/rs1799752, *ACE2* rs2285666, *APOE* rs429358, *CCR5* rs333, *IFITM3* rs12252, *TMPRSS2* rs12329760, and *TNFA* rs1800629) involving 15,550 cases and 444,007 controls were included in the meta-analyses to explore the association with SARS-CoV-2 infection risk. In the overall analysis, no significant increase in SARS-CoV-2 infection risk was found with *ACE2*

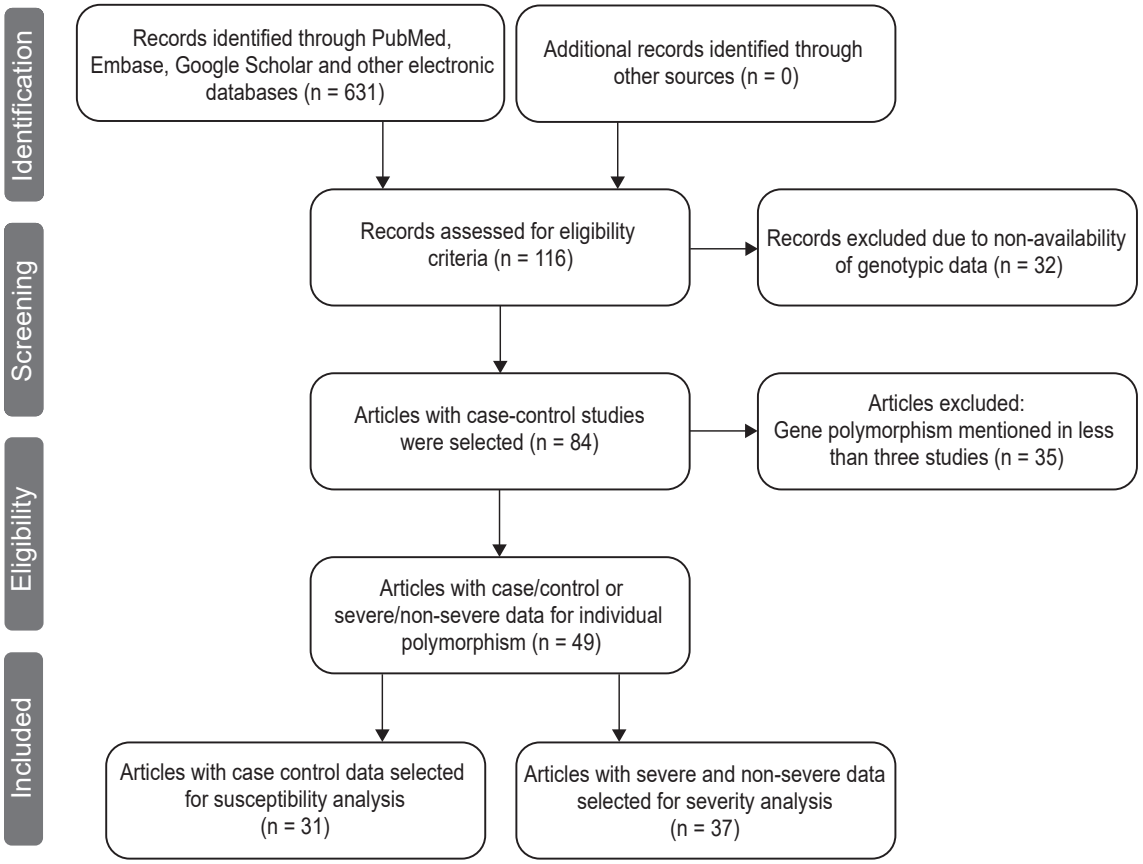

Fig. 1. PRISMA flow diagram for selection of studies for meta-analysis.

rs2285666 or *TMPRSS2* rs12329760 or *TNFA* rs1800629. However, significant increase in SARS-CoV-2 infection risk was found with *ACE1* I/D rs4646994/rs1799752, *APOE* rs429358, *CCR5* rs333, and *IFITM3* rs12252. The details of the meta-analyses results are shown in **Supplementary** Table 1 and the forest plots indicating the odds ratio with class intervals and the corresponding *P* values are given in Fig. 2. Results of publication bias and the corresponding funnel plots are provided in **Supplementary** Fig. 1**.**

***ACE1* I/D rs4646994/rs1799752:** Thirteen studies with 2400 cases and 5291 controls were included to examine the association of *ACE1* I/D rs4646994/rs1799752 with COVID-19 susceptibility. Of all the genetic models tested, significant associations were found in the allele contrast D vs I: OR = 1.36 [95 % CI (1.06, 1.73)]; P = **0.015**, the genotype contrasts DD vs II: OR = 1.76 [95 % CI (1.08, 2.86)]; P = **0.022**, the recessive model, DD vs II + ID, OR = 1.40 [95 % CI (1.00, 1.96]; P = **0.049**, and the dominant model, DD + ID vs II, OR = 1.55 [95 % CI (1.04, 2.29)]; P = **0.030**. However, no significant increase in SARS-CoV-2 infection risk was found in the genotype contrasts DD vs ID, II vs ID, and DD + II vs ID. The observed heterogeneity I^2 values were in the range of 83.9–89 %, indicating extreme inter-study heterogeneity. Publication bias was not observed for any of the models.

***APOE* rs429358:** Three datasets with 1232 cases and 323,327 controls were included to test the association of *APOE* rs429358 with susceptibility to SARS-CoV-2 infection. Of all the genetic models tested, significant associations were found in the allele contrast E4 vs E3: OR = 1.31 [95 % CI (1.18, 1.47)]; $P <$ **0.0001**, the genotype contrasts E4E4 vs E3E3: OR = 2.36 [95 % CI (1.77, 3.14)]; $P <$ **0.0001**, E4E4 vs E3E4, OR = 2.09 [95 % CI (1.55, 2.82)]; $P <$ **0.0001**, the recessive model, E4E4 vs E3E3 + E3E4: OR = 2.28 [95 % CI (1.71, 3.02)]; $P <$ **0.0001,** and the dominant model, E4E4 + E3E4 vs E3E3, OR = 1.25 [95 % CI (1.10, 1.43)]; P = **0.001**. However, no significant increase in SARS-CoV-2 infection risk was found in the genotype contrasts E3E3 vs E3E4 and E4E4 + E3E3 vs E3E4. The observed heterogeneity I^2 values were in the range of 0–25 %, indicating low inter-study heterogeneity. Publication bias for this genetic polymorphism could not be examined because of low number of studies.

***CCR5* rs333:** Four studies with 7047 cases and 108,522 controls were included in this meta-analysis. A significant increase in SARS-CoV-2 infection risk was found in the allele contrast WT vs Δ32, OR = 1.30 [95 % CI (1.00, 1.68)]; P = **0.046**. However, none of the genotype contrasts indicated any significant association. Extreme heterogeneity (I^2 = 80.9 %) was found for allelic contrast. Although, Begg-Muzumdar test indicated significant publication bias (Kendell's tau = -1, $P <$ **0.0001**), Egger's test showed no publication bias with P = 0.097.

***IFITM3* rs12252:** Three studies with 1034 cases and 875 controls were included in this meta-analysis. The association between *IFITM3* rs12252 and SARS-CoV-2 infection showed significantly increased risk in the allele contrast C vs T: OR = 1.90 [95 % CI (1.35, 2.67)]; $P =$ **< 0.001,** homozygous contrast CC vs TT: OR = 5.87 [95 % CI (1.05, 32.76)]; P = **0.044**, the genotype contrast TT vs TC: OR = 0.61 [95 % CI (0.43, 0.87)]; P = **0.006,** the recessive model, CC vs CT + TT, OR = 5.65 [95 % CI (1.01, 31.52)]; P = **0.048**, the dominant model, CC + CT vs TT: OR = 1.79 [95 % CI (1.26, 2.55)]; P = **0.001**, and the over-dominant model, CC + TT vs TC: OR = 0.61 [95 % CI (0.43, 0.88)]; P = **0.007.** Begg-Muzumdar and Egger's test did not show any publication bias.

3.3.2. Meta-analyses of genetic variants with COVID-19 severity

Eleven genetic polymorphisms (*ACE1* I/D rs1799752/rs4646994, *ACE2* rs2285666, *ACE2* rs2106809, *ACE2* rs2074192, *AGTR1* rs5186, *IFITM3* rs12252, *IFNL3/4* rs12979860, *IFNL4* rs368234815, *TMPRSS2* rs12329760, *TNFA* rs1800629, and *VDR* rs731236) involving 6702 patients with severe COVID-19 and 8640 infected individuals with non-severe manifestation were included in the meta-analyses to explore the genetic risks associated with progression to severe disease. In the

Table 2
Genotype and allele distribution of studies included in meta-analyses for COVID-19 susceptibility.

Gene, polymorphism First author, year	Distribution of genotypes						Frequency of alleles (%)				Ref.
	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	
ACE1 I/D rs4646994/ rs1799752	II		ID		DD		I		D		
Gómez, 2020	22	85	107	256	75	195	151 (37.01)	426 (39.74)	257 (62.99)	646 (60.26)	(Gómez et al., 2020 Dec)
Hubacek, 2021	107	547	210	1331	91	701	424 (51.96)	2425 (47.01)	392 (48.04)	2733 (52.99)	(Hubacek et al., 2021 Aug)
Kouhpayeh, 2021	25	51	89	123	144	70	139 (26.94)	225 (46.11)	377 (73.06)	263 (53.89)	(Kouhpayeh et al., 2021 Nov 17)
Mahmood, 2022	14	8	46	47	39	41	74 (37.37)	63 (32.81)	124 (62.63)	129 (67.19)	(Mahmood et al., 2022 Feb)
Mir, 2021	16	40	44	50	57	60	76 (32.48)	130 (43.33)	158 (67.52)	170 (56.67)	(Mir et al., 2021 Oct 27)
Akbari, 2022	4	21	70	37	17	33	78 (42.86)	79 (43.41)	104 (57.14)	103 (56.59)	(Akbari et al., 2022 Feb)
Calabrese, 2021	5	13	25	50	38	48	35 (25.74)	76 (34.23)	101 (74.26)	146 (65.77)	(Calabrese et al., 2021 Jan)
Saad, 2021	33	12	104	72	95	71	170 (36.64)	96 (30.97)	294 (63.36)	214 (69.03)	(Saad et al., 2021 Dec)
Möhlendick, 2021	66	58	126	118	105	77	258 (43.43)	234 (46.25)	336 (56.57)	272 (53.75)	(Möhlendick et al., 2021 Oct 1)
Aladag, 2021	8	128	59	95	45	77	75 (33.48)	351 (58.5)	149 (66.51)	249 (41.5)	(Aladag et al., 2021 Sep)
Gong, 2022	116	156	177	228	128	57	409 (48.57)	540 (61.22)	433 (51.42)	342 (38.77)	(Gong et al., 2021)
Papadopoulou, 2021	13	51	21	150	39	115	47 (32.19)	252 (39.87)	99 (67.80)	380 (60.12)	(Papadopoulou et al., 2022 Mar)
Annunziata, 2021	1	3	2	8	17	8	4 (10)	14 (36.84)	36 (90)	24 (63.15)	(Annunziata et al., 2021 Aug 20)
***ACE2* rs2285666**	**GG**		**GA**		**AA**		**G**		**A**		
Mahmood, 2022	26	33	17	14	6	1	69 (70.41)	80 (83.33)	29 (25.59)	16 (16.67)	(Mahmood et al., 2022 Feb)
Gómez, 2020	45	174	28	81	6	9	118 (74.68)	429 (81.25)	40 (25.32)	99 (18.75)	(Gómez et al., 2020 Dec)
Möhlendick, 2021	230	178	40	35	27	40	500 (84.18)	391 (77.27)	94 (15.82)	115 (22.73)	(Möhlendick et al., 2021 Oct 1)
Alimoradi, 2022	66	24	11	19	2	7	143 (90.50)	67 (67)	15 (9.49)	33 (33)	(Alimoradi et al., 2022 Mar 19)
***APOE* rs429358**	**E3E3**		**E3E4**		**E4E4**		**E3**		**E4**		
Kuo, 2020	401	223,056	184	90,285	37	8985	986 (79.26)	536,397 (83.21)	258 (20.74)	108,255 (16.79)	(Kuo et al., 2020 May 26)
Al-Jaf, 2021	77	92	15	8	0	0	169 (91.85)	192 (96.00)	15 (8.15)	8 (4.00)	(Al-Jaf et al., 2021 Nov)
Hilser, 2021	342	636	144	242	32	23	828 (79.92)	1514 (84.02)	208 (20.08)	288 (15.98)	(Hilser et al., 2021 Jan)
***CCR5* rs333**	**WT/WT**		**WT/Δ32**		**Δ32/Δ32**		**WT**		**Δ32**		
Cuesta- Llavona, 2021	705	539	96	106	0	5	1506 (94.01)	1184 (91.08)	96 (5.99)	116 (8.92)	(Cuesta-Llavona et al., 2021 Sep)
Bernas, 2021	4458	83,883	1012	19,886	66	1239	9928 (89.67)	187,652 (89.35)	1144 (10.33)	22,364 (10.65)	(Bernas et al., 2021 Apr)
Gómez, 2020	264	375	30	81	0	4	558 (94.90)	831 (90.33)	30 (5.10)	89 (9.67)	(Gómez et al., 2020)
Hubacek, 2021	335	1899	76	464	5	41	746 (89.66)	4262 (88.64)	86 (10.34)	546 (11.36)	(Hubacek et al., 2021 Mar 17)
***IFITM3* rs12252**	**CC**		**CT**		**TT**		**C**		**T**		
Schönfelder, 2021	2	0	22	19	215	234	26 (5.44)	19 (3.75)	452 (94.56)	487 (96.25)	(Schönfelder et al., 2021 Jun)
Gómez, 2021	3	0	32	26	276	414	38 (6.11)	26 (2.95)	584 (93.89)	854 (97.05)	(Gómez et al., 2021 Jan)
Cuesta- Llavona, 2021	4	0	47	10	433	172	55 (5.68)	10 (2.75)	913 (94.32)	354 (97.25)	(Cuesta-Llavona et al., 2021)
***TMPRSS2* rs12329760**	**CC**		**CT**		**TT**		**C**		**T**		
Andolfo, 2021	696	2563	277	1051	23	149	1669 (83.79)	6177 (82.09)	323 (16.21)	1349 (17.92)	(Andolfo et al., 2021)
Schönfelder, 2021	139	164	84	78	16	11	362 (75.73)	406 (80.24)	116 (24.27)	100 (19.76)	(Schönfelder et al., 2021 Apr)
Ravikanth, 2021	269	277	212	180	29	43	750 (73.53)	734 (73.40)	270 (26.47)	266 (26.60)	(Ravikanth et al., 2021 Sep)
Rokni, 2022	61	90	145	147	82	51	267 (46.35)	327 (56.77)	309 (53.64)	249 (43.22)	(Rokni et al., 2022 Apr)
***TNFA* rs1800629**	**GG**		**GA**		**AA**		**G**		**A**		
Ali, 2022	87	93	37	17	1	4	211 (84.4)	203 (89.03)	39 (15.6)	25 (10.96)	(Ali et al., 2022 May)
Nia, 2021	104	76	135	139	36	60		291 (52.90)		259 (47.09)	(Heidari Nia et al., 2022)

(*continued on next page*)

Table 2 (*continued*)

Gene, polymorphism First author, year	Distribution of genotypes						Frequency of alleles (%)				Ref.
	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	
ACE1 I/D rs4646994/ rs1799752	II		ID		DD		I		D		
Saleh, 2020	192	84	288	40	420	60	343 (62.36) 672 (37.33)	208 (56.52)	207 (37.63) 1128 (62.66)	160 (43.47)	(Saleh et al., 2020 Nov)

overall analysis, the following polymorphisms did not exhibit statistically significant association with severe COVID-19: *ACE1* I/D rs1799752/rs4646994, *IFITM3* rs12252, *IFNL3/4* rs12979860, *IFNL4* rs368234815, *TMPRSS2* rs12329760, and *VDR* rs731236. However, patients with *ACE2* rs2285666, *ACE2* rs2106809, *ACE2* rs2074192, *AGTR1* rs5186 and *TNFA* rs1800629 were found to have increased risk of severe COVID-19. The details of the meta-analyses results are shown in **Supplementary** Table 2 and the forest plots indicating the odds ratio with class intervals and the corresponding *P* values are given in Fig. 3. Results of publication bias and the corresponding funnel plots are provided in **Supplementary** Fig. 2.

***ACE2* rs2285666:** Seven studies with 550 severe and 600 non-severe cases were included in the meta-analysis to test the association of *ACE2* rs2285666 with severe COVID-19. Although the allele and homozygous contrasts did not show any association, significant association was detected for the genotype contrasts AA vs GA: OR = 2.27 [95 % CI (1.42, 3.64)]; $P = \mathbf{0.001}$, GG vs GA, OR = 1.57 [95 % CI (1.10, 2.24)]; $P = \mathbf{0.013}$, and AA + GG vs GA: OR = 1.72 [95 % CI (1.24, 2.41)]; $P = \mathbf{0.001}$. However, no association with severe COVID-19 was found in the other genetic models. No heterogeneity was detected for the genetic contrasts that showed significant association with severe COVID-19. Begg-Mazumdar and Egger's test did not show any publication bias.

***ACE2* rs2106809:** Three studies with 281 severe and 210 non-severe cases were included in this meta-analysis. Although the allele contrast did not show any association, significant association was detected for the genotype contrasts GG vs AA: OR = 1.82 [95 % CI (1.02, 3.25)]; $P = \mathbf{0.041}$, GG vs AG, OR = 2.40 [95 % CI (1.07, 5.38)]; $P = \mathbf{0.033}$, and the recessive model, GG vs AA + AG: OR = 1.92 [95 % CI (1.09, 3.40)]; $P = \mathbf{0.025}$. However, no association with severe COVID-19 was found in the other genetic models. Although large heterogeneity was found for the allele contrast (I^2 = 57 %), no heterogeneity was detected for the other genetic contrasts that showed significant association with severe COVID-19. Publication bias could not be calculated due to insufficient number of studies.

***ACE2* rs2074192:** Four studies with 609 severe and 476 non-severe cases were included in this meta-analysis. Similar to the results of the above meta-analyses for *ACE2* polymorphisms, no association with severe COVID-19 was detected in the allele contrast. The homozygote contrast did not show any association either. Significant association was detected for the genotype contrasts TT vs CT: OR = 3.28 [95 % CI (1.33, 8.06)]; $P = \mathbf{0.010}$, CC vs CT, OR = 2.16 [95 % CI (1.51, 3.07)]; $P < \mathbf{0.0001}$, and TT + CC vs CT: OR = 2.42 [95 % CI (1.67, 3.51)]; $P < \mathbf{0.0001}$. However, no association with severe COVID-19 was found in the other genetic models. High heterogeneity was found to exist in the genotype contrast TT vs CT, but no heterogeneity was detected for the other genetic contrasts that showed significant association with severe COVID-19. Publication bias was not detected in any of the models.

***AGTR1* rs5186:** Three studies with 387 severe and 233 non-severe cases were included in this meta-analysis. A significant increase in the risk of severe COVID-19 was found in the allele contrast A vs C: OR = 1.49 [95 % CI (1.13–1.98)]; $P = \mathbf{0.005}$. Although the comparison of AA and CC genotype generated a 21.1 % increased risk for COVID-19 severity, the association was not statistically significant: OR = 2.11 [95 % CI (0.98, 4.57)]; $P = 0.057$. However, significant association was detected for the heterozygote contrast AA vs CA, OR = 1.53 [95 % CI (1.07, 2.19)]; $P = \mathbf{0.02}$, the recessive model, AA vs CC + CA, OR = 1.60 [95 % CI (1.13, 2.26)]; $P = \mathbf{0.007}$, and the co-dominant model, AA + CC vs CA, OR = 1.42 [95 % CI (1.00, 2.02)]; $P = \mathbf{0.049}$. No heterogeneity was found in any of the genetic contrasts tested. Publication bias was not found in any of the models.

***TNFA* rs1800629:** Four studies with 693 severe cases and 638 non-severe cases were included in this meta-analysis. No association with severe COVID-19 was found in allele, genotype, recessive and dominant contrasts. Also, the I^2 values were in the range of 82.8–96.3 %, indicating extreme inter-study heterogeneity. Significant association was found in over-dominant model AA + GG vs GA: OR = 1.50 [95 % CI (1.12, 1.99)]; $P = \mathbf{0.006}$. No heterogeneity was found for this model. Publication bias was not detected in any of these models.

4. Discussion

In this comprehensive review, we systematically searched all the studies that investigated the association between genetics variants and the risk of SARS-CoV-2 infection and progression to severe COVID-19. Through a systematic search of the candidate gene-based case-control association studies, we recapitulated the body of evidence about the risks associated with the genetic variants for infection and progression to severe disease conditions. In this study, we excluded the reports on polymorphisms present in vicinity of the *HLA* genes as they have been extensively reviewed (Di Maria et al., 2020; Ferreira de Araújo et al., 2022; Sáenz Hinojosa and Romero, 2021; SeyedAlinaghi et al., 2021; Deb et al., 2022 Apr). In the screening phase, we identified 84 studies that examined the association of 130 polymorphisms in 61 genes with COVID-19. Next, we conducted meta-analysis of the genetic polymorphisms for which at least three studies were available. In total, 7 and 11 meta-analyses were performed to explore the association of the genetic variants with COVID-19 susceptibility and severity, respectively.

Recently, two meta-analyses evaluated the influence of the polymorphisms in *ACE1*, *ACE2*, and *TMPRSS2* (Saengsiwaritt et al., 2022 Jan) and *ACE1*; *IFITM3*, *FURIN*, and *TNF A* (de Araújo et al., 2022) on susceptibility to SARS-CoV-2 infection. However, these studies represented only a subset of potential genetic biomarkers that have been assessed for conferring risk to COVID-19. Since the number of genetic association studies on COVID-19 has rapidly grown over the last two years, compilation of all the reported evidence and their statistical evaluation became a worthwhile necessity. In this systematic review and meta-analysis, we identified, appraised and synthesized all the relevant studies, and quantitatively estimated the association of several genetic polymorphisms with COVID-19 risk and severity. Although we initially identified 130 genetic polymorphisms that were evaluated for conferring risk to COVID-19, we could perform meta-analyses for 7 and 11 polymorphisms for COVID-19 susceptibility and severity, respectively. The rest of the polymorphisms lacked sufficient number of studies to conduct statistical analysis of association. We performed updated meta-analyses for the polymorphisms that were evaluated for association with COVID-19 in the previous meta-analyses (de Araújo et al., 2022; Saengsiwaritt et al., 2022). Our study unveiled statistically significant associations between the polymorphisms *ACE1* I/D rs1799752/ rs4646994, *APOE* rs429358, *CCR5* rs333, and *IFITM3* rs12252 and susceptibility to SARS-CoV-2 infection. We also found the

Table 3
Genotype and allele distribution of studies included in meta-analyses for COVID-19 severity.

Gene, polymorphism First author, year	Distribution of genotypes						Frequency of alleles (%)				Ref.
	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	
***ACE1* I/D rs4646994/ rs1799752**	**II**		**ID**		**DD**		**I**		**D**		
Gómez, 2020	5	17	31	76	31	44	41 (30.60)	110 (40.15)	93 (69.40)	164 (59.85)	(Gómez et al., 2020 Dec)
Molina, 2022	44	16	74	36	95	44	162 (38.03)	68 (35.42)	264 (61.97)	124 (64.58)	(Sabater Molina et al., 2022)
Hubacek, 2021	71	36	123	87	51	40	265 (54.08)	159 (48.77)	225 (45.92)	167 (51.23)	(Hubacek et al., 2021 Aug)
Kouhpayeh, 2021	10	15	58	31	84	60	78 (25.66)	61 (28.77)	226 (74.34)	151 (71.23)	(Kouhpayeh et al., 2021 Nov 17)
Verma, 2021	42	74	48	58	30	17	132 (55.00)	206 (69.13)	108 (45.00)	92 (30.87)	(Verma et al., 2021 Jul)
Akbari, 2022	0	4	31	39	6	11	31 (41.89)	47 (43.52)	43 (58.11)	61 (56.48)	(Akbari et al., 2022 Feb)
Möhlendick, 2021	19	47	40	86	31	74	78 (43.33)	180 (43.48)	102 (56.67)	234 (56.52)	(Möhlendick et al., 2021 Oct 1)
Cafiero, 2021	7	22	15	21	32	7	29 (26.85)	65 (65.00)	79 (73.15)	35 (35.00)	(Cafiero et al., 2021 May)
Gong, 2022	24	92	43	134	36	92	91 (44.17)	318 (50)	115 (55.82)	318 (50)	(Gong et al., 2021)
Gunal, 2021	9	22	2	12	19	26	20 (33.33)	56 (46.66)	40 (66.66)	64 (53.33)	(Gunal et al., 2021 Jun)
Martínez-Gómez, 2022	121	62	157	64	54	23	399 (60.09)	188 (63.08)	265 (39.90)	110 (36.91)	(Martínez-Gómez et al., 2022 Feb)
Çelik, 2021	6	21	15	64	14	34	27 (38.57)	106 (44.53)	43 (61.42)	132 (55.46)	(Karakaş Çelik et al., 2021 Oct)
Serdal Baştuğ, 2022	11	7	21	30	18	13	43 (43)	44 (44)	57 (57)	56 (56)	(Baştuğ et al., 2021 Dec 8)
Mahmood, 2022	5	9	13	33	13	26	23 (37.09)	51 (37.5)	39 (62.90)	85 (62.5)	(Mahmood et al., 2022 Feb)
Mir, 2021	11	5	20	24	12	45	42 (48.83)	34 (22.97)	44 (51.16)	114 (77.02)	(Mir et al., 2021 Oct 27)
Saad, 2021	5	28	26	74	30	60	36 (29.50)	130 (40.12)	86 (70.49)	194 (59.87)	(Saad et al., 2021 Dec)
***ACE2* rs2285666**	**GG**		**GA**		**AA**		**G**		**A**		
Gómez, 2020	9	36	3	25	2	4	21 (75.00)	97 (74.62)	7 (25.00)	33 (25.38)	(Gómez et al., 2020 Dec)
Möhlendick, 2021	80	150	6	34	4	23	166 (92.22)	334 (80.68)	14 (7.78)	80 (19.32)	(Möhlendick et al., 2021 Oct 1)
Molina, 2022	25	33	12	10	7	1	62 (70.45)	76 (86.36)	26 (29.55)	12 (13.64)	(Sabater Molina et al., 2022)
Çelik, 2021	7	30	6	27	1	6	20 (71.43)	87 (69.05)	8 (28.57)	39 (30.95)	(Karakaş Çelik et al., 2021 Oct)
Alimoradi, 2022	38	28	5	6	1	1	81 (92.04)	62 (88.57)	7 (7.95)	8 (11.42)	(Alimoradi et al., 2022 Mar 19)
Martínez-Gómez, 2022	165	76	47	38	120	35	377 (56.77)	190 (63.75)	287 (43.22)	108 (36.24)	(Martínez-Gómez et al., 2022 Feb)
Mahmood, 2022	7	19	4	13	1	5	18 (75)	51 (68.91)	6 (25)	23 (31.08)	(Mahmood et al., 2022 Feb)
***ACE2* rs2106809**	**AA**		**AG**		**GG**		**A**		**G**		
Cafiero, 2021	40	38	3	4	11	8	83 (76.85)	80 (80.00)	25 (23.15)	20 (20.00)	(Cafiero et al., 2021 May)
Çelik, 2021	9	28	3	28	2	7	21 (75.00)	84 (66.67)	7 (25.00)	42 (33.33)	(Karakaş Çelik et al., 2021 Oct)
Molina, 2022	148	77	21	11	44	9	317 (74.41)	165 (85.05)	109 (25.59)	29 (14.95)	(Sabater Molina et al., 2022)
***ACE2* rs2074192**	**CC**		**CT**		**TT**		**C**		**T**		
Martínez-Gómez, 2022	164	69	51	39	117	41	379 (57.07)	177 (59.39)	285 (42.92)	121 (40.60)	(Martínez-Gómez et al., 2022 Feb)
Cafiero, 2021	27	28	7	21	20	1	61 (56.48)	77 (77)	47 (43.51)	23 (23)	(Cafiero et al., 2021 May)
Molina, 2022	111	41	32	31	70	24	254 (59.62)	113 (58.85)	172 (40.37)	79 (41.14)	(Sabater Molina et al., 2022)
Wang, 2022	5	79	2	46	3	56	12 (60)	204 (56.35)	8 (40)	158 (43.64)	(Wang et al., 2022 Jan)
***AGTR1* rs5186**	**AA**		**AC**		**CC**		**A**		**C**		
Kouhpayeh, 2021	96	58	23	26	1	3	215 (89.58)	142 (81.61)	25 (10.42)	32 (18.39)	(Kouhpayeh et al., 2021 Nov 17)
Cafiero, 2021	35	27	17	21	2	2	87 (80.56)	75 (75.00)	21 (19.44)	25 (25.00)	(Cafiero et al., 2021 May)

(*continued on next page*)

Table 3 (*continued*)

Gene, polymorphism First author, year	Distribution of genotypes						Frequency of alleles (%)				Ref.
	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	
Molina, 2022	114	43	86	43	13	10	314 (73.71)	129 (67.19)	112 (26.29)	63 (32.81)	(Sabater Molina et al., 2022)
***IFITM3* rs12252**	**TT**		**TC**		**CC**		**T**		**C**		
Zhang, 2020	5	10	8	30	14	16	18 (33.33)	50 (44.64)	36 (66.67)	62 (55.36)	(Zhang et al., 2020 Jul 1)
Schönfelder, 2021	68	147	7	15	0	2	143 (95.33)	309 (94.21)	7 (4.67)	19 (5.79)	(Schönfelder et al., 2021 Jun)
Gómez, 2021	69	297	10	22	2	1	148 (91.36)	616 (96.25)	14 (8.64)	24 (3.75)	(Gómez et al., 2021 Jan)
Alghamdi, 2021	330	372	73	82	1	3	733 (90.72)	826 (90.37)	75 (9.28)	88 (9.63)	(Alghamdi et al., 2021 Jul)
Cuesta- Llavona, 2021	133	300	17	30	2	2	283 (93.09)	630 (94.87)	21 (6.90)	34 (5.12)	(Cuesta-Llavona et al., 2021)
***IFNL3/4* rs12979860**	**CC**		**CT**		**TT**		**C**		**T**		
Rahimi, 2021	27	275	178	91	170	9	232 (30.93)	641 (85.47)	518 (69.07)	109 (14.53)	(Rahimi et al., 2021 Dec)
Agwa, 2021	51	41	35	32	9	9	137 (72.11)	114 (69.51)	53 (27.89)	50 (30.49)	(Agwa et al., 2021 May 28)
Amodio, 2020	57	101	73	109	19	22	187 (62.75)	311 (67.03)	111 (37.25)	153 (32.97)	(Amodio et al., 2020 Oct 15)
Grimaudo, 2021	24	135	24	159	5	36	72 (67.92)	429 (65.00)	34 (32.08)	231 (35.00)	(Grimaudo et al., 2021 Jun)
***IFNL4* rs368234815**	**ΔG/ΔG**		**ΔG/TT**		**TT/TT**		**ΔG**		**TT**		
Amodio, 2020	17	17	58	86	47	75	92 (37.70)	120 (33.71)	152 (62.30)	236 (66.29)	(Amodio et al., 2020 Oct 15)
Rahimi, 2021	154	8	193	97	28	270	501 (66.80)	113 (15.07)	249 (33.20)	637 (84.93)	(Rahimi et al., 2021 Dec)
Grimaudo, 2021	4	30	21	123	22	101	29 (30.85)	183 (36.02)	65 (69.15)	325 (63.98)	(Grimaudo et al., 2021 Jun)
***TMPRSS2* rs12329760**	**CC**		**CT**		**TT**		**C**		**T**		
Schönfelder, 2021	48	91	23	61	4	12	119 (79.33)	243 (74.09)	31 (20.67)	85 (25.91)	(Schönfelder et al., 2021 Apr)
Wulandari, 2021	13	29	10	23	7	13	36 (60.00)	81 (62.31)	24 (40.00)	49 (37.69)	(Wulandari et al., 2021)
Ravikanth, 2021	56	213	36	176	0	29	148 (80.43)	602 (72.01)	36 (19.57)	234 (27.99)	(Ravikanth et al., 2021 Sep)
Rokni, 2022	27	34	103	42	56	26	157 (42.20)	110 (53.92)	215 (57.79)	94 (46.07)	(Rokni et al., 2022 Apr)
***TNFA* rs1800629**	**GG**		**GA**		**AA**		**G**		**A**		
Ali, 2022	36	51	16	21	0	1	88 (84.61)	123 (84.24)	16 (15.38)	23 (15.75)	(Ali et al., 2022 May)
Nia, 2021	53	20	85	56	41	20	191 (53.35)	96 (50)	167 (46.64)	96 (50)	(Heidari Nia et al., 2022)
Saleh, 2020	0	192	120	168	336	84	120 (13.15)	552 (62.16)	792 (86.840)	336 (37.83)	(Saleh et al., 2020 Nov)
Fishchuk, 2021	4	18	2	5	0	2	10 (83.33)	41 (82)	2 (16.66)	9 (18)	(Fishchuk et al., 2021 Dec 6)
***VDR* rs731236**	**TT**		**TC**		**CC**		**T**		**C**		
Fishchuk, 2021	0	12	6	11	0	2	6 (50)	35 (70)	6 (50)	15 (30)	(Fishchuk et al., 2021 Dec 6)
Apaydin, 2021	37	83	41	89	7	10	115 (67.64)	255 (70.05)	55 (32.35)	109 (29.94)	(Apaydin et al., 2022 Jun)
Abdollahzadeh, 2021	51	208	29	152	10	50	131 (72.77)	568 (69.26)	49 (27.22)	252 (30.73)	(Abdollahzadeh et al., 2021 Dec)

polymorphisms *ACE2* rs2285666, *ACE2* rs2106809, *ACE2* rs2074192, *AGTR1* rs5186, and *TNFA* rs1800629 to be associated with increased risk of developing severe disease manifestations. Recent genome-wide association studies (GWASs) identified association of *ACE2*, *TMPRSS2*, *CCR5*, and *APOE* variants with susceptibility to SARS-CoV-2 infection (Baranova et al., 2021; Karlsen, 2022; Thibord et al., 2022). However, the studies did not find association with *ACE1*, *IFITM3*, *AGTR1*, and *TNFA*. While GWAS is a powerful tool to uncover the genetic variants associated with a disease, applying hypothesis-free and non-candidate gene approach, it can also lead to the identification of false negative/positive associations. To minimize detection of spurious associations and verify negative findings, very large sample size is required to achieve optimal statistical power in GWAS. Identification of many genetic variants may remain elusive if GWAS is restricted to a single population, and not replicated in independent populations to include genetic diversity. Furthermore, the findings through GWAS can be impacted by linkage disequilibrium, which may vary among populations, and may lead to biased results (Sirugo et al., 2019; Sesia et al., 2021 Oct 5). The above factors can account for the fact that some of the genetic variants that have been identified in this meta-analysis of candidate gene-based studies, remained elusive in GWAS.

In the cellular entry of SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2) serve as the receptor and S protein priming factor, respectively (Hoffmann et al., 2020 Apr 16). Although ACE2 is an entry receptor of SARS CoV-2, it also counter balances ACE1-mediated renin-angiotensin system (RAS) via ACE2/Ang (1-7)/MAS axis (Ni et al., 2020 Jul 13). Therefore, any alteration either in the ACE1/ACE2 expression

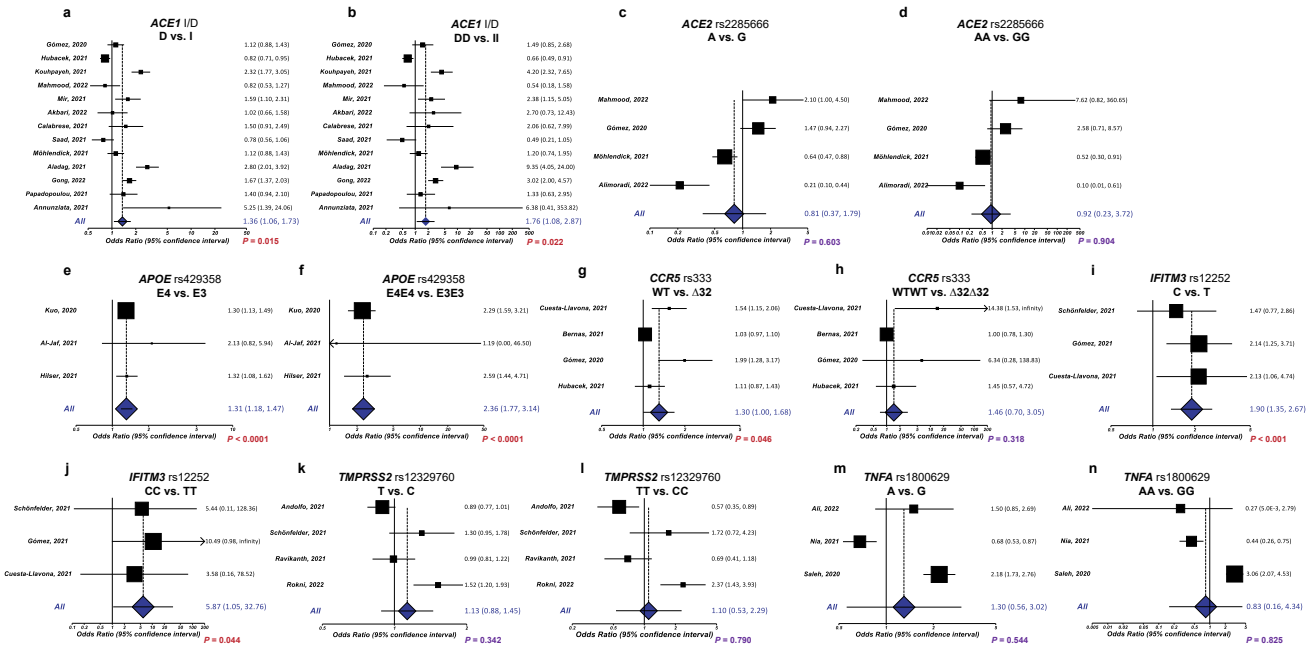

Fig. 2. Forest plots of meta-analyses of association of genetic polymorphisms with SARS-CoV-2 susceptibility. Genetic contrasts shown are (a) *ACE* I/D, D vs I (b) *ACE* I/D, DD vs II (c) *ACE2* rs2285666, A vs G (d) *ACE2* rs2285666, AA vs GG (e) *APOE* rs429358, E4 vs E3 (f) *APOE* rs429358, E4E4 vs E3E3 (g) *CCR5* rs333, WT vs Δ32 (h) *CCR5* rs333, WTWT vs Δ32Δ32 (i) *IFITM3* rs12252, C vs T (j) *IFITM3* rs12252, CC vs TT (k) *TMPRSS2* rs12329760, T vs C (l) *TMPRSS2* rs12329760, TT vs CC (m) *TNFA* rs1800629, A vs G (n) *TNFA* rs1800629, AA vs GG.

levels or signalling axis can lead to COVID-19 manifestations (Pagliaro and Penna, 2020 Jun). ACE1 expression was found to be modulated by an insertion/deletion (I/D) of 287-bp Alu repeat in the intron 16 of *ACE1* (Delanghe et al., 2020 Jun). This Alu element in intron16 plays a regulatory role by interacting with *ACE1* promoter region. Deletion of this element enhances ACE1 levels in the serum (Wu et al., 2013 Jul). Polymorphisms in *ACE2* (rs2285666, rs2106809, rs2074192), *TMPRSS2* (rs12329760), and *ACE1* (I/D, rs1799752/rs4646994) were regarded as confounders in COVID-19 spread. Our meta-analyses did not show any significant association of *ACE2* rs2285666 and *TMPRSS2* rs12329760 with COVID-19 susceptibility. However, our data indicated that the individuals with *ACE1* D allele and DD genotype are more susceptible to SARS-CoV-2 infection than the carriers of I allele and II genotype.

APOE encodes the lipoprotein Apo E, which is a multifunctional protein involved in lipid metabolism and is also associated with cardiovascular and neurodegenerative diseases (Poirier et al., 1993; Huang and Apolipoprotein, 2014). The isoforms of *APOE*, namely *APOE2*, *APOE3*, and *APOE4* are consequences of three alleles *ε2*, *ε3*, and *ε4*, respectively, of this polymorphic gene. These three isoforms are differentiated based on amino acids present at 112 and 158 positions (Tudorache et al., 2017 Jan). *APOE E4* was found to be associated with infectious diseases including HCV, HIV, and HSV infections (Kuhlmann et al., 2010 Jan). ApoE4 binds to the low density lipoprotein receptor (LDL-R), a receptor for HCV for cellular entry, with highest affinity, followed by E3 and E2. Therefore, binding of HCV to LDL-R is compromised in the presence of ApoE4 due to competitive binding to the receptor, resulting in reduced viral entry. Moreover, E4 is associated with progression of both HIV and HSV, but with different underlying mechanisms. ApoE4 binds to the HIV envelope and directs the virus towards LDL-R, facilitating its entry into the host cell. Since HSV enters the host cell through lipid rafts enriched in cholesterol, HSV entry in the E4 carriers is promoted due to high LDL expression and enrichment of cholesterol in lipid rafts on the plasma membrane. Also, binding of ApoE with heparan sulphate proteoglycans on the cell surface plays an important role in HIV and HSV infections (Kuhlmann et al., 2010 Jan). The E4 carriers show elevated levels of circulating and tissue-specific cholesterol, and increased LDL level in pneumocytes and lung macrophages, which lead to an increased accumulation of ACE2 and TMPRSS2 in cholesterol-enriched domains/lipid rafts. Thus, cholesterol enrichment can be a critical factor determining the likelihood of SARS-CoV-2 infection in pneumocytes and lung macrophages (Gkouskou et al., 2021 May).

In our meta-analysis, a comparison of *APOE* E4E4 and E3E3 genotypes generated a 23.6 % increased risk for SARS-CoV-2 infection. The E4E4 genotype was also found to increase infection risk by 20.9 % and 22.8 % when compared with the genotypes E3E4 and E3E3 + E3E4, respectively. Significant increase in COVID-19 susceptibility was also found in the allele contrast.

The C—C motif chemokine receptor 5 (CCR5) serves as a predominant co-receptor for HIV-1 entry and facilitates cell-to-cell virus transmission (Allers and Schneider, 2015 Oct). A 32-nucleotide deletion mutation in *CCR5*, known as *CCR*5 Δ32, leads to appearance of premature stop codon which results in a truncated protein, impairing CCR5 expression on the cell surface and protecting the homozygous subjects against HIV-1 infection (Liu et al., 1996; Ellwanger et al., 2020). The *CCR*5 Δ32 polymorphism was also found to be associated with increased susceptibility to infections with influenza virus, West Nile virus, and HCV (Ellwanger et al., 2020). Interestingly, *CCR*5 Δ32 was found to confer genetic protection against dengue virus and HBV infections (Abdolmohammadi et al., 2016; Marques et al., 2015; Thio et al., 2007). Administration of Leronlimab, a CCR5-specific monoclonal antibody, reduces overactivation of immune system upon COVID-19 infection, indicating protective role of *CCR*5 *Δ32* in COVID-19 susceptibility (Patterson et al., 2021 Feb). Our study also indicated a protective role of the *CCR*5 Δ32 allele against COVID-19. However, this result should be considered with caution due to extreme inter-study heterogeneity.

IFITM3 encodes for the interferon-induced transmembrane protein 3, which restricts infection by many viruses including influenza A virus, SARS-CoV, HIV, HCV, Ebola virus, vesicular stomatitis virus, and Zika virus (Spence et al., 2019 Mar). IFITM3 is present in the detergent-resistant microdomains of endo-lysosomal membranes and it regulates cholesterol homeostasis. The antiviral action of this protein is mediated by its dimerization on the endo-lysosomal membranes and making the fusion pore formation energetically unfavourable, preventing

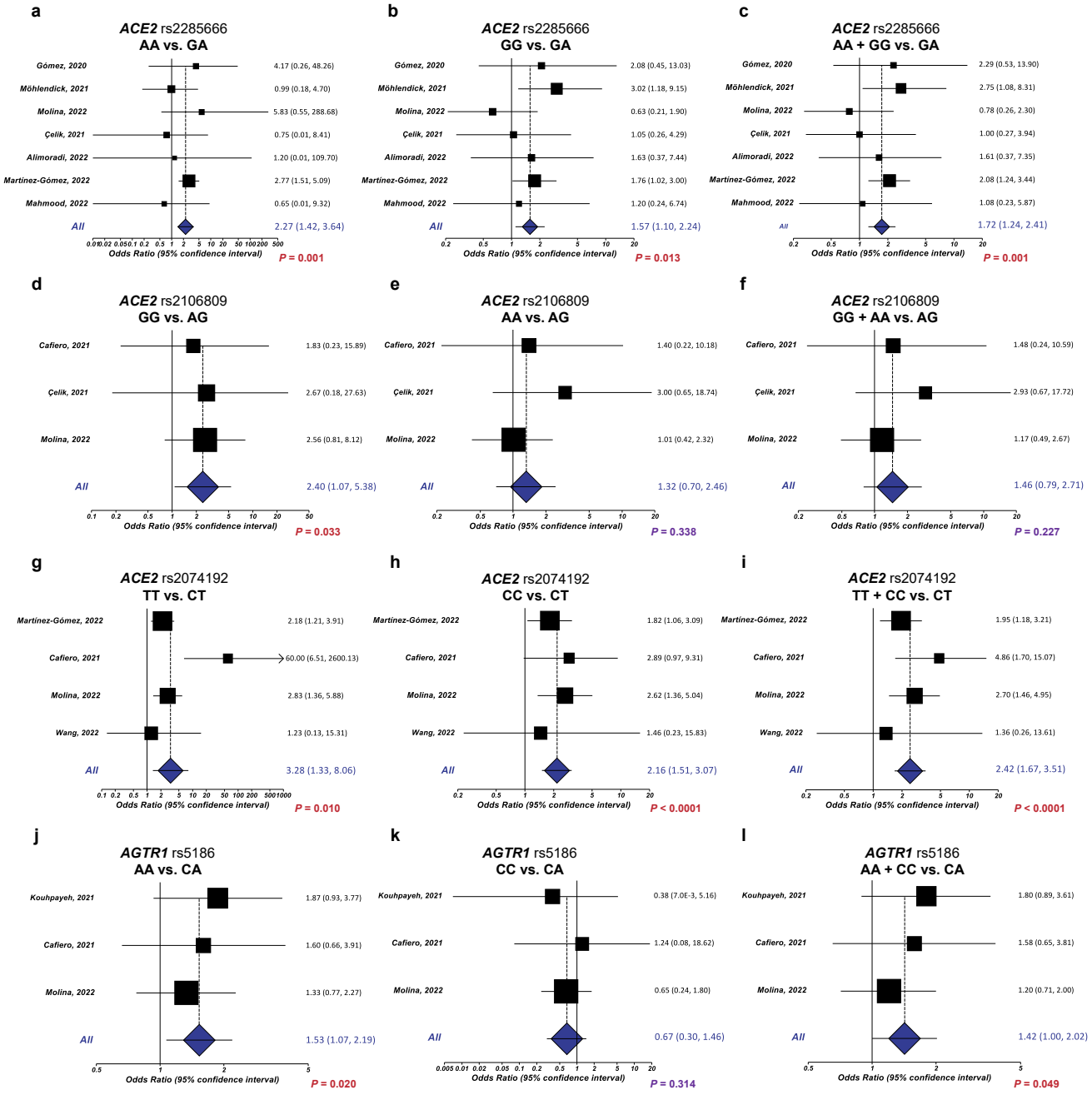

Fig. 3. Forest plots of meta-analyses of association of genetic polymorphisms with SARS-CoV-2 severity. Genetic contrasts shown are: (a) *ACE2* rs2285666, AA vsGA (b) *ACE2* rs2285666, GG vsGA (c) *ACE2* rs2285666, AA + GG vs GA (d) *ACE2* rs2106809, GG vs AG (e) *ACE2* rs2106809, AA vs AG (f) *ACE2* rs2106809, GG + AA vs AG (g) *ACE2* rs2074192, TT vs CT (h) *ACE2* rs2074192, CC vs CT (i) *ACE2* rs2074192, TT + CC vs CT (j) *AGTR1* rs5186, AA vs CA (k) *AGTR1*, rs5186 CC vs CA (l) *AGTR1*, rs5186 AA + CC vs CA.

hemifusion and viral escape into the cytoplasm (Bailey et al., 2014 Nov). The SNP rs12252 causes alteration in the splice acceptor site, leading to the formation of a truncated protein lacking the first 21 amino acids in the *N*-terminal region. The mislocalization and structure alteration render the protein incapable of its antiviral activity. Our previous meta-analysis revealed an association of *IFITM3* rs12252 (T > C polymorphism) with susceptibility to influenza (Prabhu et al., 2018 Oct). In the present study, we found that the *IFITM3* rs12252 C allele and CC genotype confer 19 % and 58.7 % increased chance of SARS-CoV-2 infection when compared with the T allele and TT genotype, respectively. The CC genotype also showed a 56.5 % increased risk for COVID-19 when compared with the carriers of TT and TC genotypes. Of note, no heterogeneity between individual studies was found for any of the genetic contrasts for this polymorphism. The association of *IFITM3* rs12252 with increased risk of infection can be attributed to the compromised antiviral activity of IFITM3 in the carriers of this mutation.

Although the *ACE1* I/D polymorphism showed significant association with COVID-19 susceptibility, no association was detected when the polymorphism was tested for association with severe disease manifestation. Interestingly, the homozygotes of *ACE2* rs2285666 and rs2074192 showed significant association with COVID-19 severity when compared with the respective heterozygotes. *ACE2* rs2285666 (G8790A) is present in the splice site of intron 3, and the G > A substitution renders a stronger splice site, enhancing ACE2 expression by almost 50 % (Asselta et al., 2020; Wu et al., 2016). Therefore, the

heterozygotes of rs2285666 express intermediate levels of ACE2 receptor, suggesting a protective role against progression to severe disease. Similar observations were found for another intronic polymorphism rs2074192 for which, both the homozygotes showed association with disease severity. *ACE2* rs2074192 is present in intron 16 and is known to be responsible for lower levels of Ang (1-7) in circulation (Bosso et al., 2020; Hamet et al., 2021). Another polymorphism, rs2106809, is present in intron 1, which also reduces the circulating levels of Ang (1-7). However, whether rs2074192 and rs2106809 have any direct consequence in altering ACE2 level remain to be determined (Fan et al., 2007; Rusmini et al., 2021). The GG genotype of *ACE2* rs2106809 showed significant association with COVID-19 severity when compared with the other homozygote i.e. AA or the heterozygote. Significant association observed in the recessive model further indicates that the carriers of GG genotype are at higher risk of progressing to severe COVID-19.

In addition to *ACE2* polymorphisms, we also found significant association of *AGTR1* rs5186 with severe COVID-19. *AGTR1* encodes for the angiotensin II receptor type 1, a protein of the renin-angiotensin system. This receptor is stimulated by angiotensin II, which is formed by the enzymatic action of ACE1 on its substrate angiotensin I. Once activated, this G-protein coupled receptor initiates downstream signalling via activation of serine/threonine kinases and receptor tyrosine kinases leading to vasoconstriction, hypertrophy, fibrosis or inflammation in tissues (Forrester et al., 2018 Jul 1). Upon ACE2-mediated SARS-CoV-2 internalization into the host cell, the ACE2 expression is downregulated in the infected cell. Reduced ACE2 level leads to an increase in angiotensin II level as angiotensin II is converted to angiotensin III and Ang (1-7) by an aminopeptidase and ACE2, respectively. The elevated angiotensin II level causes AGTR1 activation, which subsequently triggers NF-κB signalling and expression of inflammatory cytokines. AGTR1 and angiotensin II interaction also induces cytokine expression in macrophages, often leading to cytokine storm, exaggerating COVID-19 pathogenesis (Banu et al., 2020 Sep). The *AGTR1* rs5186 polymorphism (A1166C), located at the 3′ UTR of the gene, influences the expression of the gene and affects the stability of mRNAs (Braliou et al., 2014 Jun). Abdollahi *et al.* reported that the carriers of C allele or CC homozygotes have reduced level of *AGTR1* mRNAs (Abdollahi et al., 2007 Apr). Also, the *AGTR1* rs5186 C allele was found to be associated with increased risk of essential hypertension (Bonnardeaux et al., 1994 Jul). Our study indicates, the carriers of the A allele or AA genotype are at higher risk of progressing to severe COVID-19 as compared to the individuals with the C allele or CA genotype, which corroborates with the fact that the reduced AGTR1 levels in these individuals may lead to less severe diseases.

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine which initiates immune signalling cascades leading to its anti-viral and cytotoxic effects in cells **(**Idriss and Naismith, 2000; Seo and Webster, 2002**)**. TNF-α acts as mediator for innate and adaptive immune system. *TNFA* rs1800629 is marked by transition of G to A at position −308. TNF-α expression is regulated at the promoter region where various other polymorphisms either upregulate or downregulate its expression. *TNFA* rs1800629 has been associated with increased TNF-α production, leading to altered immune homeostasis (Khan et al., 2016 Dec). Role of this polymorphism (rs1800629) has been previously reported in disease progression of HBV and influenza A virus (Basturk et al., 2008; Saud et al., 2016; Tayebi and Mohamadkhani, 2012). SARS-CoV-2 is known to induce hyper- inflammatory response, which includes upregulation of TNF-α, interleukin (IL)-6, IL-1, and IL-12, leading to severe disease conditions (Costela-Ruiz et al., 2020 Aug). Some clinical trials suggested protective role of anti-TNF drugs against COVID-19 progression (Guo et al., 2022 Feb). In the present study, we found that combining AA and GG genotypes pose 15 % more risk to severe COVID-19.

The other polymorphisms (*IFITM3* rs12252, *IFNL3/4* rs12979860, *IFNL4* rs368234815, *TMPRSS2* rs12329760, and *VDR* rs731236) did not show any significant association with COVID-19 severity.

Although this systematic review and meta-analysis contribute to our current understanding of the host genetic determinants of COVID-19 susceptibility and severity, the findings have some caveats that should be considered and weighted for limitations. First, despite an extensive literature search, the possibility of missing some relevant articles cannot be disregarded. To reduce the risk of missing relevant articles, we updated the search multiple times to identify the latest reports and extensively hand-searched the reference lists of the published articles. Since we limited our search to articles in English and articles that were published, studies in other languages and unpublished data were renounced, which might potentially bias the findings. Second, the critical covariates like age, sex, and comorbidities, which account for the variability in COVID-19 manifestations were not considered. Disregarding the confounding factors that are recognized as cardinal mediators for clinical manifestation of the disease, might influence the results by contributing to heterogeneity. Third, although the body of evidence on potential genetic biomarkers of COVID-19 susceptibility and severity is rapidly growing, the number of case-control association studies that have been reported so far is still very limited. Therefore, meta-analyses could only be performed of a subset of polymorphisms that have been studied and identified in this study. Moreover, the outcomes of the meta-analyses might have suffered from low statistical power due to paucity of data for each polymorphism. Fourth, the data included in this meta-analysis were not stratified by host genetic background or ethnicity as the number of studies from different geographical locations were limited. Therefore, future investigations are recommended in genealogically-varied populations from different geographical locations. Finally, considering the interdependence of genes in pathways implicated in complex clinical manifestations, the results of single gene analysis might be masked by other gene-gene interactions. To overcome this intrinsic constraint, future studies with more robust methodological approaches are warranted to explore the interactions of multiple genetic risk factors contributing to SARS-CoV-2 infection susceptibility and increasing the risk of life-threatening complications.

In conclusion, to the best of our knowledge, this is the most extensive systematic review till date and the first meta-analysis with the largest available dataset providing the most comprehensive empirical evidence of all genetic association studies on COVID-19. This study presented statistical evaluation of association of several genetic polymorphisms with COVID-19 susceptibility and severity by combining pertinent quantitative study data. Altogether, we identified 84 studies, which examined the association of 130 polymorphisms in 61 genes with COVID-19. Seven genetic polymorphisms including 15,550 infected patients and 444,007 uninfected individuals were evaluated for association with COVID-19 susceptibility, which revealed that *ACE1* I/D rs1799752/rs4646994, *APOE* rs429358, *CCR5* rs333, and *IFITM3* rs12252 are associated with increased the risk of SARS-CoV-2 infection. Association with COVID-19 severity was investigated for 11 genetic variants, including 6702 patients with severe illness and 8640 asymptomatic infected individuals or infected patients with mild symptoms. Our data indicate significant association of *ACE2* rs2285666, *ACE2* rs2106809, *ACE2* rs2074192, *AGTR1* rs5186, and *TNFA* rs1800629 with severe clinical manifestations. However, future epidemiological studies in genetically diverse populations with larger sample size are still warranted to corroborate our findings. Identification of the genetic determinants of COVID-19 susceptibility and severity might be crucial to elucidate the underlying biological pathways, detect the susceptible individuals, and pave the way in designing promising therapeutic strategies for COVID-19.

Availability of data and materials.

The datasets used/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions.

This study was conceptualized by IB. Systematic literature search, data collection and meta-analyses were performed equally by KG, GK, and TP. The manuscript was written and reviewed by KG, GK, TP, and

IB, and approved by all authors.

Funding sources

This study was supported by an intramural research funding from IISER Mohali.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

KG was supported by a research fellowship from the Council of Scientific and Industrial Research (CSIR), Govt. of India, GK was supported by a research fellowship from the University Grants Commission (UGC), Govt. of India, and TP was supported by a research fellowship from IISER Mohali.

Ethics approval and consent to participate.

Not applicable

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2022.146790.

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