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Association of genetic polymorphisms with COVID-19 infection and outcomes: An updated meta-analysis based on 62 studies

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ABSTRACT

Background: The relationship between genetic polymorphisms and coronavirus disease 2019 (COVID-19) remains to be inconsistent. This meta-analysis aimed to provide an updated evaluation of the role of genetic polymorphisms in the infection, severity and mortality of COVID-19 based on all available published studies.

Methods: A systematic search was performed using six databases: PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wanfang. Summary odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) were used to calculate the genotypic comparison. All statistical analyses were conducted in Stata 12.0.

Results: A total of 62 studies with 19600 cases and 28899 controls was included in this meta-analysis. For COVID-19 infection, *ACE* Ins/Del polymorphism might be related with significantly decreased risk of COVID-19 infection under dominant, homozygote and allelic models. Meanwhile, the *IFITM3* rs12252 and *TMPRSS2* rs12329760 polymorphisms were significantly associated with the increased risk of COVID-19 infection under one or more models. Regarding COVID-19 severity, *ACE2* rs2074192, *ACE2* rs2106809, *IFITM3* rs12252 and *VDR* rs1544410 polymorphisms might be related with significantly increased risk of COVID-19 severity in one or more models. Moreover, the analysis of *TMPRSS2* rs2070788 indicated that a variant A allele decreased the risk of COVID-19 severity in recessive model. For COVID-19 mortality, the variant C allele of *IFITM3* rs12252 polymorphism might be related with significantly increased risk of COVID-19 mortality under all genetic models.

Conclusions: This meta-analysis indicated that he infection, severity or mortality of COVID-19 were related to the above genetic polymorphisms, which might provide an important theoretical basis for understanding the clinical feature of COVID-19 disease.

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1. Introduction

Coronavirus disease 2019 (COVID-19), known as severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), is a rapidly infectious disease caused by a novel coronavirus emerging from the end of 2019 [1]. Due to the infection of COVID-19, it has spread worldwide and currently affects more than 200 countries. Although massive public health measures and vaccination initiatives are applied against COVID-19, there is currently no effective treatment for patients who have developed severe lung injury [2]. Worryingly, COVID-19 remains still a major challenge for public health worldwide, resulting in huge social and economic burdens. Hence, it is urgent to uncover the pathogenic mechanism of COVID-19.

It's worth noting that the clinical course and severity of COVID-19 patients exist distinct individual differences, ranging from asymptomatic to severe pneumonia

with multiple organ failure. Some studies indicate that the development and severity of COVID-19 patients have been linked to different clinical risk factors, including old, male and previous comorbidities [3,4]. Increasingly, researchers have focused on the role of host genetic factors in the progression and severity of COVID-19 disease including angiotension converting enzyme (*ACE*), interleukin 6 (*IL6*), tumor necrosis factor α (*TNFα*), interferon-induced transmembrane protein 3 (*IFITM3*), interferon lambda type 3 (*IFNL3*), transmembrane serine protease 2 (*TMPRSS2*), vitamin D receptor (*VDR*) and so on [5]. However, there is inconsistency between these findings. Furthermore, the same genetic polymorphism might have different effects on the infection, severity or mortality of COVID-19. For example, some studies showed that *TMPRSS2* rs12329760 polymorphism was positive related to SARS-CoV-2 infection risk or severity of COVID-19 [6,7]. On the contrary, some articles indicated that *TMPRSS2* rs12329760 polymorphism was associated with a reduced risk of COVID-19 disease [8,9].

Although several meta-analyses analyzed the relationship between *ACE*, *TMPRSS2*, and *IFITM3* polymorphisms with COVID-19 risk [10,11], many new studies including different gene locus variants [12,13] and the same locus variants of *ACE*, *TMPRSS2* and *IFITM3* with larger populations [6,14,15] have been published. Therefore, we conducted an updated meta-analysis to analyze the association of genetic polymorphisms with COVID-19 infection and outcomes.

2. Materials and methods

The meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement [16].

2.1. Search strategy

Electronic databases including PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wanfang were comprehensively searched with time span from inception to December 20, 2022. The following keywords and MeSH terms were used in each database: polymorphism, genetic, gene, COVID-19, Coronavirus Disease 2019, SARS-CoV-2 Infection. The detailed search results in PubMed were summarized in Supplemental Table 1. The literatures were preliminarily screened by assessing titles and abstracts, and then retrieved in full text to evaluate for eligibility.

2.2. Definition of disease severity

There were a lot of different classifications of COVID-19 severity by individual studies and these differences can influence the reproducing of the results. Hence, this meta-analysis accepted all definitions of COVID-19 severity by individual studies and reclassified all patients into two groups (non-severe and severe) based on WHO COVID-19 disease severity classification in order to match the World Health Organization guidelines [17]. Specifically, severe disease patients require oxygen support, and 5 % have critical disease with complications such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury. Subgroups analysis were performed to recognize the differences.

2.3. Definition of control groups

For infection, this meta-analysis accepted all definitions of non-infection groups by individual studies including healthy volunteers, PCR negative, and pre-pandemic population controls. Subgroups analysis was performed to recognize these differences.

2.4. Inclusion and exclusion criteria

Eligible articles should meet all the following criteria: (1) studies about the relationship between genetic polymorphisms and COVID-19 directly and indirectly; (2) a case-control or cohort study; (3) literatures providing sufficient data including genotypes and sample size; (4) English or Chinese articles. Exclusive criteria were as follows: (1) reviews, meta-analyses, conference abstracts, letters or commentaries; (2) literatures without sufficient data; (3) only one or two reports of a genotype; (4) data not available.

2.5. Data extraction and quality assessment

Two authors extracted the useful information independently in accordance with a standardized extraction, and any discrepancies

were solved by discussion or consulting a third author if needed. The extracted data mainly included as follows:

the first author, publication time, country, ethnicity, genotyping method, genetic polymorphisms, outcomes of COVID-19, genotype counts in the case and the control group, the Hardy-Weinberg equilibrium (HWE) of the controls. The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the eligible studies [18]. The quality assessment values ranged from 0 to 9 stars. Studies that scored ≥5 were defined as high quality, and 0–4 stars were regarded as low quality respectively.

2.6. Statistical analysis

Data analyzing and processing were performed using STATA version 12.0 (Stata Corp, College Station, TX, USA). Four gene models were evaluated, which were the dominant model (MM + MW vs. WW), recessive model (MM vs. MW + WW), homozygote model (MM vs. WW), and Allelic model (M vs. W) (M: mutation allele, W: wild allele). Genotype frequencies of the control group were analyzed by HWE using the Chi-square test. Summary odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) were calculated using a random effect model. Heterogeneity among studies was tested using Cochran's Q-test and I^2 statistics, and values of $I^2 \geq 50$ % or $P \leq 0.05$ indicated significant heterogeneity. Subgroup analyses based on ethnicity and study quality were performed to investigate the source of heterogeneity. Sensitivity analysis was conducted to assess the effect of individual study on pooled results through deleting a single study each time. Egger's test and Begg's test were adopted to evaluate the publication bias. All tests were two-sided and $P < 0.05$ was supposed to have a statistically significance.

3. Results

3.1. Characteristics of included studies

Flowchart of the study selection process was shown in Fig. 1. A total of 2337 records (PubMed, 656; Embase, 189; Web of Science,

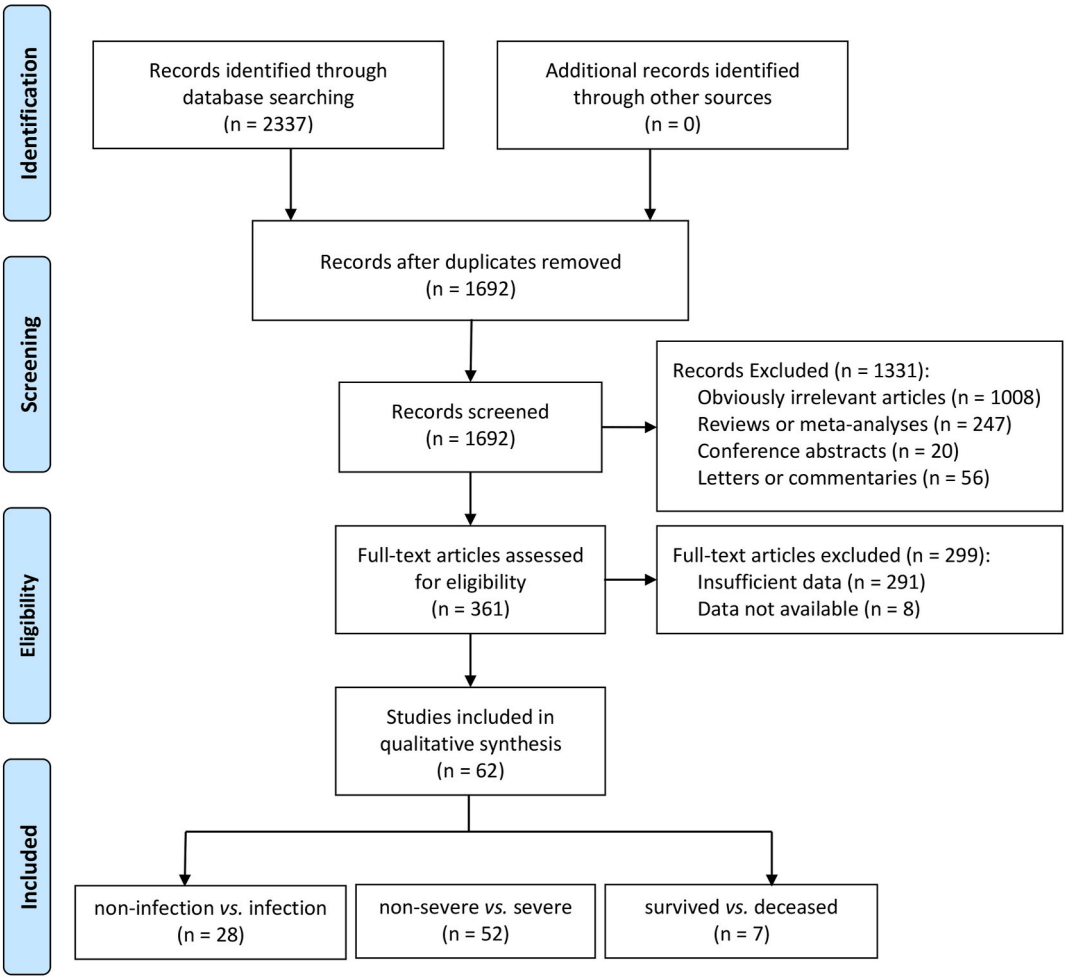

Fig. 1. Flow chart of study selection.

Table 1
Main characteristics of included studies in the meta-analysis.

Study [Reference]	Country	Ethnicity	Genotype Method	COVID-19 outcomes and SNP	NOS score	Quality
Abbaszadeh 2022 [19]	Iran	Caucasian	PCR-AFLP	Infection: *ACE1* rs1799752; severity: *ACE1* rs1799752	5	High
Abdelsattar 2022 [6]	Egypt	Mixed	TaqMan SNP genotyping assay	Infection and severity: *ACE2* rs2285666, *TMPRSS2* rs12329760	5	High
Abdollahzadeh 2021 [20]	Iran	Caucasian	PCR-RFLP	Severity: *VDR* rs7975232, rs1544410, rs2228570, rs731236	4	Low
Agwa 2021 [21]	Egypt	Mixed	TaqMan SNP genotyping assay	Severity: *IFNL3* rs12979860	6	High
Ahmadi 2022 [15]	Iran	Caucasian	Sequencing	Severity and mortality: *IFITM3* rs12252	6	High
Akbari 2022 [14]	Iran	Caucasian	Sequencing	Infection and severity: *ACE1* rs1799752	5	High
Aladag 2021 [22]	Turkey	Caucasian	PCR-AFLP	Infection and severity: *ACE* Ins/Del	5	High
Aladawy 2022 [23]	Egypt	Mixed	TaqMan SNP genotyping assay	Severity: *IL6* rs1800795	6	High
Al-Anouti 2021 [24]	UAE	Mixed	Infinium global screening array	Severity: *VDR* rs7975232, rs1544410, rs2228570, rs731236	5	High
Alghamdi 2021 [25]	Saudi Arabia	Asian	Fluorescence prove assay	Severity and mortality: *IFITM3* rs12252	5	High
Ali 2022 [12]	Iraq	Caucasian	PCR-AFLP	Severity: *TNFα* rs1800629	5	High
Alimoradi 2022 [26]	Iran	Caucasian	PCR-RFLP	Infection and severity: *ACE2* rs2285666	5	High
Amodio 2020 [27]	Italy	Caucasian	TaqMan SNP genotyping assay	Severity: *IFNL3* rs12979860	8	High
Andrade 2022 [35]	Brazil	Caucasian	TaqMan SNP genotyping assay	Severity: *TMPRSS2* rs2070788, rs12329760; Mortality: *TMPRSS2* rs12329760	8	High
Angulo-Aguado 2022 [28]	Colombia	Mixed	Sequencing	Infection: *ACE1* rs4646994, *ACE2* rs2285666	8	High
Annunziata 2021 [29]	Italy	Caucasian	PCR-AFLP	Infection: *ACE* Ins/Del	5	High
Apaydin 2021 [30]	Turkey	Caucasian	PCR-RFLP	Severity: *VDR* rs7975232, rs1544410, rs2228570, rs731236	5	High
Balzanelli 2022 [31]	Italy	Caucasian	PCR-AFLP	Infection: *ACE1* rs1799752, *VDR* rs2228570	5	High
Baştuğ 2021 [32]	Turkey	Caucasian	PCR-AFLP	Severity: *ACE1* rs1799752	7	High
Cafiero 2021 [34]	Italy	Caucasian	Commercial kits	Severity: *ACE1* rs1799752; *ACE2* rs2074192, rs2106809	4	Low
Çelik 2021 [44]	Turkey	Caucasian	PCR-RFLP	Severity: *ACE* Ins/Del; *ACE2* rs2106809, rs2285666	5	High
Falahi 2022 [36]	Iran	Caucasian	PCR-RFLP	Severity: *IL6* rs1800795, rs1800797	5	High
Faridzadeh 2022 [37]	Iran	Caucasian	PCR-RFLP	Infection and severity: *ACE1* rs1799752	6	High
Gómez 2020 [39]	Spain	Caucasian	PCR-AFLP	Infection and severity: *ACE1* rs4646994, *ACE2* rs2285666	5	High
Gómez 2021 [38]	Spain	Caucasian	Sequencing	Infection and severity: *IFITM3* rs12252	5	High
Gong 2022 [40]	China	Asian	PCR-AFLP	Infection and severity: *ACE* Ins/Del	4	Low
Gunal 2021 [41]	Turkey	Caucasian	PCR-AFLP	Severity: *ACE* Ins/Del	6	High
Hubacek 2021 [42]	Czech Republic	Caucasian	PCR-AFLP	Infection and severity: *ACE1* rs4646994	5	High
Jafarpoor 2022 [13]	Iran	Caucasian	PCR-AFLP	Infection: *VDR* rs2228570	4	Low
Jevnikar 2022 [43]	Slovenia	Caucasian	KASPar genotyping chemistry with validated assays	Infection: *ACE1* rs4646994, *ACE2* rs2285666	5	High
Kerget 2021 [45]	Turkey	Caucasian	Allele-specific SNP type assays	Severity: *IL6* rs1800795, rs1800797	4	Low
Khalilzadeh 2022 [46]	Iran	Caucasian	PCR-RFLP	Severity: *ACE2* rs2285666	5	High
Kotur 2021 [47]	Serbia	Caucasian	TaqMan SNP genotyping assay	Severity: *VDR* rs2228570	5	High
Lapić 2022 [48]	Croatia	Caucasian	Commercial multilocus genotyping assays	Severity: *ACE* Ins/Del	5	High
Mahdi 2022 [49]	Iraq	Caucasian	Sequencing	Severity: *TMPRSS2* rs2070788, rs12329760	5	High
Martínez-Gómez 2022 [50]	Mexico	Mixed	TaqMan SNP genotyping assay	Severity: *ACE* Ins/Del; *ACE2* rs2074192, rs2285666	4	Low
Mir 2021 [51]	Saudi Arabia	Caucasian	PCR-AFLP	Infection and severity: *ACE1* rs4646994	5	High
Möhlendick 2021 [52]	Germany	Caucasian	Sequencing	Infection and severity: *ACE1* rs1799752, *ACE2* rs2285666	4	Low
Molina 2022 [62]	Spain	Caucasian	Sequencing	Severity: *ACE* Ins/Del; *ACE2* rs2074192, rs2106809, rs2285666	5	High
Najafi 2022 [53]	Iran	Caucasian	Sequencing	Severity: *ACE1* rs4646994, *ACE2* rs2285666	4	Low
Nhung 2022 [54]	Vietnam	Asian	Sequencing	Infection and severity: *TMPRSS2* rs12329760	7	High
Pan 2021 [55]	China	Asian	Sequencing	Infection and severity: *IFITM3* rs12252	5	High
Papadopoulou 2021 [56]	Greece	Caucasian	PCR-AFLP	Infection: *ACE1* rs1799752	5	High
Peralta 2021 [57]	Cuba	Mixed	PCR-RFLP	Severity: *VDR* rs731236	5	High

(*continued on next page*)

Table 1 (*continued*)

Study [Reference]	Country	Ethnicity	Genotype Method	COVID-19 outcomes and SNP	NOS score	Quality
Posadas-Sánchez 2022 [9]	Mexico	Mixed	TaqMan SNP genotyping assay	Infection: *TMPRSS2* rs12329760	5	High
Rahimi 2021 [58]	Iran	Caucasian	PCR-RFLP	Severity: *IFNL3* rs12979860	6	High
Reviono 2022 [59]	Indonesia	Asian	PCR-AFLP	Severity: *TNFα* rs1800629	7	High
Rokni 2022 [60]	Iran	Caucasian	PCR-AFLP	Infection, severity and mortality: *TMPRSS2* rs12329760	8	High
Saad 2021 [61]	Lebanon	Caucasian	PCR-AFLP	Infection and severity: *ACE1* rs1799752	5	High
Saleh 2020 [63]	Egypt	Mixed	TaqMan SNP genotyping assay	Severity: *TNFα* rs1800629	4	Low
Schönfelder 2021 (1) [64]	Germany	Caucasian	Sequencing	Infection and severity: *IFITM3* rs12252	7	High
Schönfelder 2021 (2) [65]	Germany	Caucasian	PCR-RFLP	Infection and severity: *TMPRSS2* rs12329760; Severity: *TMPRSS2* rs2070788	8	High
Sekiya 2022 [8]	Japan	Asian	Sequencing	Infection and severity: *TMPRSS2* rs12329760	5	High
Shirazi 2022 [33]	Iran	Caucasian	Sequencing	Severity and mortality: *TMPRSS2* rs12329760	6	High
Sienko 2022 [66]	Poland	Caucasian	PCR-AFLP	Severity: *ACE2* rs2074192, rs2285666	4	Low
Sotomayor-Lugo 2022 [67]	Cuba	Mixed	PCR-AFLP	Severity: *TNFα* rs1800629	5	High
Verma 2021 [68]	India	Mixed	PCR-AFLP	Severity: *ACE1* rs4646994	7	High
Verma 2022 [69]	India	Mixed	PCR-RFLP	Severity: *IL6* rs1800795, rs1800797	4	Low
Vitello 2022 [7]	Italy	Caucasian	Sequencing	Infection: *TMPRSS2* rs12329760	5	High
Wulandari 2021 [70]	Indonesia	Asian	TaqMan SNP genotyping assay	Severity and mortality: *TMPRSS2* rs12329760	6	High
Zeidan 2022 [71]	Egypt	Mixed	Allelic discrimination RT-PCR	Infection and severity: *VDR* rs2228570	5	High
Zhang 2020 [72]	China	Asian	Sequencing	Severity and mortality: *IFITM3* rs12252	6	High

Annotation: ACE: angiotensin-converting enzyme type; AFLP: amplified fragment length polymorphism; COVID-19: coronavirus disease 2019; IFITM3: interferon-induced transmembrane protein 3; IFNL3: interferon lambda type 3; IL6: interleukins-6; NOS: Newcastle-Ottawa scale; RFLP: restriction fragment length polymorphism; RT-PCR: real-time reverse transcription polymerase chain reaction; SNP: single nucleotide polymorphism; TMPRSS2: transmembrane serine protease type 2; TNFα: tumor necrosis factor-α; UAE, United Arab Emirates; VDR: vitamin D receptor.

718; Cochrane Library, 22; CNKI, 311; Wanfang, 441) were preliminarily identified according to our search strategy. Of these, 1692 records remained after removing duplicates. And then, 361 records screened after reading titles and abstracts. Finally, 62 records included in this meta-analysis after a full text screen, which contained 19600 cases and 28899 controls [6–9,12–15,19–72]. Among them, 28 records with 8296 cases and 8822 controls were eligible on the association between COVID-19 infection and genetic polymorphisms including seven SNPs in the four genes (*ACE* Ins/Del, *ACE1* rs1799752, *ACE1* rs4646994, *ACE2* rs2285666, *IFITM3* rs12252, *TMPRSS2* rs12329760, *VDR* rs2228570); 52 records with 9975 cases and 17250 controls were selected to estimate the association between COVID-19 severity and genetic polymorphisms including seventeen SNPs in the seven genes (*ACE* Ins/Del, *ACE1* rs1799752, *ACE1* rs4646994, *ACE2* rs2074192, ACE2 rs2106809, ACE2 rs2285666, IFITM3 rs12252, IFNL3 rs12979860, IL6 rs1800795, IL6 rs1800797, TMPRSS2 rs12329760, TMPRSS2 rs2070788, TNFα rs1800629, VDR rs1544410, VDR rs2228570, VDR rs731236, VDR rs7975232); 7 records with 1329 cases and 2827 controls were selected to assess the association between COVID-19 mortality and genetic polymorphisms including *IFITM3 rs12252* and *TMPRSS2* rs12329760. The main characteristics of the 62 articles were shown in Table 1. Of these, 41 articles were performed in Caucasian populations, 13 articles in mixed populations, and 8 articles in Asian populations. For the detection of genotype method, 19 articles were using PCR-AFLP, 15 articles using sequencing, 11 articles using PCR-RFLP, 10 articles using TaqMan SNP genotyping assay, other articles using Allele-specific SNP type assays, KASPar genotyping chemistry with validated assays and so on. For the quality of included studies, 51 articles were regarded as high quality, and 11 articles were considered as low quality. Genotype frequencies of control groups in all studies were calculated by the HWE test (Supplemental Table 2). In addition, control groups of included studies for COVID-19 infection in the meta-analysis were summarized in Supplemental Table 3.

3.2. Meta-analysis results

The meta-analysis results of the association between genetic polymorphisms with the infection, severity and mortality of COVID-19 were presented in Table 2. Subgroup analysis was performed according to ethnicity and study quality if the included studies were greater than or equal to five (Supplemental Table 4).

3.2.1. Genetic polymorphisms with COVID-19 infection

Our meta-analysis showed that the variant I allele of *ACE* Ins/Del polymorphism might be related with significantly decreased risk of COVID-19 infection under dominant (II + ID vs. DD, OR = 0.37, 95 % CI: 0.24–0.59, $P < 0.001$, Fig. 2A), homozygote (II vs. DD, OR = 0.20, 95 % CI: 0.08–0.49, $P = 0.001$, Fig. 2B) and allelic models (I vs. D, OR = 0.42, 95 % CI: 0.25–0.69, $P = 0.001$, Fig. 2C). The *IFITM3* rs12252 polymorphism was significantly associated with the risk of COVID-19 infection under allelic model (C vs. T, OR =

Table 2
Meta-analysis of the association of genetic polymorphisms with COVID-19 infection and outcomes.

Study group	Study (n)	Dominant model			Recessive model			Homozygote model			Allelic model		
		OR (95%CI)	P	I2 (%)	OR (95%CI)	P	I2 (%)	OR (95%CI)	P	I2 (%)	OR (95%CI)	P	I2 (%)
Infection *vs.* Non-infection													
ACE Ins/Del	3	**0.37 (0.24–0.59)**	**<0.001**	50.2	0.28 (0.06–1.36)	0.114	91.1	**0.20 (0.08–0.49)**	**0.001**	**68.5**	**0.42 (0.25–0.69)**	**0.001**	**79.7**
ACE1 rs1799752	7	0.93 (0.67–1.29)	0.674	64.9	0.95 (0.61–1.47)	0.821	65.5	0.92 (0.65–1.29)	0.626	33.4	0.95 (0.83–1.10)	0.516	18.7
ACE1 rs4646994	5	1.01 (0.77–1.33)	0.917	48.7	0.80 (0.50–1.29)	0.365	73.7	0.83 (0.47–1.46)	0.519	75.9	0.93 (0.71–1.21)	0.589	74.6
ACE2 rs2285666	6	0.80 (0.42–1.54)	0.504	87.6	0.78 (0.26–2.32)	0.652	89.1	0.72 (0.23–2.23)	0.570	89.2	0.82 (0.40–1.65)	0.573	93.8
IFITM3 rs12252	3	1.45 (0.97–2.16)	0.070	28.9	1.87 (0.76–4.61)	0.173	11.2	2.07 (0.65–6.55)	0.216	20.0	1.49 (1.02–2.18)	0.040	46.0
TMPRSS2 rs12329760	7	1.18 (0.93–1.49)	0.179	50.8	**1.45 (1.13–1.87)**	**0.004**	**0**	**1.46 (1.01–2.12)**	**0.042**	**31.7**	1.19 (0.98–1.44)	0.076	55.8
VDR rs2228570	3	1.01 (0.22–4.71)	0.985	93.8	0.90 (0.63–1.28)	0.560	0	0.65 (0.23–1.79)	0.401	68.9	1.16 (0.57–2.37)	0.678	88.8
Severe *vs.* Non-severe													
ACE Ins/Del	7	0.83 (0.62–1.10)	0.195	18.9	0.85 (0.66–1.09)	0.195	0	0.80 (0.59–1.08)	0.140	0	0.87 (0.74–1.02)	0.083	0
ACE1 rs1799752	7	0.76 (0.43–1.36)	0.359	77.2	0.70 (0.40–1.24)	0.220	62.9	0.59 (0.26–1.34)	0.206	76.4	0.78 (0.51–1.18)	0.237	82.0
ACE1 rs4646994	5	1.27 (0.55–2.94)	0.576	87.7	1.01 (0.50–2.04)	0.979	76.8	1.16 (0.41–3.32)	0.776	84.8	1.14 (0.66–1.96)	0.638	88.8
ACE2 rs2074192	4	1.61 (0.69–3.75)	0.267	87.6	**3.38 (1.47–7.78)**	**0.004**	**82.3**	**3.91 (1.19–12.79)**	**0.024**	**88.7**	**2.06 (1.05–4.04)**	**0.035**	**90.9**
ACE2 rs2106809	3	1.10 (0.55–2.20)	0.793	49.9	**1.92 (1.09–3.41)**	**0.025**	**0**	**1.82 (1.02–3.25)**	**0.041**	**0**	1.30 (0.73–2.31)	0.381	57.0
ACE2 rs2285666	10	0.82 (0.49–1.38)	0.447	87.0	0.87 (0.42–1.80)	0.700	85.9	0.83 (0.37–1.85)	0.651	87.2	0.84 (0.50–1.42)	0.518	92.8
IFITM3 rs12252	6	1.46 (0.67–3.17)	0.342	91.0	**3.06 (1.35–6.94)**	**0.008**	**59.9**	2.28 (0.71–7.39)	0.168	74.8	1.71 (0.81–3.61)	0.159	93.5
IFNL3 rs12979860	3	3.77 (0.29–48.22)	0.307	98.2	4.14 (0.34–49.77)	0.263	95.3	7.71 (0.20–300.04)	0.274	97.5	2.69 (0.41–17.67)	0.304	98.5
IL6 rs1800795	4	0.76 (0.30–1.92)	0.558	81.2	0.53 (0.10–2.86)	0.462	34.2	0.51 (0.08–3.06)	0.460	37.9	0.88 (0.46–1.65)	0.682	75.5
IL6 rs1800797	3	0.88 (0.58–1.35)	0.565	0.0	1.13 (0.72–1.77)	0.604	0	0.83 (0.37–1.88)	0.654	0	0.99 (0.77–1.29)	0.957	0
TMPRSS2 rs12329760	10	1.17 (0.47–2.91)	0.744	96.7	0.97 (0.43–2.03)	0.940	87.4	1.14 (0.39–3.31)	0.808	92.8	1.05 (0.52–2.13)	0.883	96.9
TMPRSS2 rs2070788	3	0.54 (0.18–1.59)	0.264	77.1	**0.60 (0.39–0.93)**	**0.023**	**0**	0.52 (0.22–1.32)	0.138	48.1	0.68 (0.42–1.09)	0.109	59.0
TNFα rs1800629	4	4.74 (0.25–88.59)	0.298	95.9	2.20 (0.20–24.14)	0.520	81.1	8.07 (0.02–3395.26)	0.498	93.5	2.05 (0.35–11.92)	0.423	96.8
VDR rs1544410	3	1.37 (0.89–2.11)	0.149	57.1	1.26 (0.87–1.82)	0.226	0	**1.56 (1.03–2.36)**	**0.038**	**0**	1.18 (0.99–1.41)	0.066	0
VDR rs2228570	5	1.02 (0.78–1.34)	0.871	0	1.03 (0.69–1.53)	0.885	22.1	1.11 (0.65–1.91)	0.707	23.7	1.00 (0.80–1.26)	0.976	27.8
VDR rs731236	4	0.96 (0.76–1.21)	0.734	0	1.28 (0.86–1.91)	0.220	0	1.23 (0.82–1.86)	0.320	0	1.03 (0.86–1.23)	0.777	0
VDR rs7975232	3	1.03 (0.77–1.39)	0.832	0	1.10 (0.77–1.58)	0.601	28.4	1.02 (0.69–1.52)	0.902	0	1.05 (0.88–1.25)	0.569	0
Deceased *vs.* Survived													
IFITM3 rs12252	3	**2.75 (1.26–6.00)**	**0.011**	**77.2**	**6.46 (4.60–9.08)**	**< 0.001**	**0**	**7.86 (4.36–14.19)**	**< 0.001**	**5.1**	**2.84 (1.17–6.88)**	**0.021**	**86.3**
TMPRSS2 rs12329760	4	0.54 (0.12–2.36)	0.415	94.9	0.44 (0.12–1.55)	0.201	83.3	0.43 (0.07–2.76)	0.373	90.0	0.53 (0.16–1.75)	0.296	96.0

Annotation: ACE: angiotensin-converting enzyme type; COVID-19: coronavirus disease 2019; IFITM3: interferon-induced transmembrane protein 3; IFNL3: interferon lambda type 3; IL6: interleukins-6; TMPRSS2: transmembrane serine protease type 2; TNFα: tumor necrosis factor-α; VDR: vitamin D receptor.

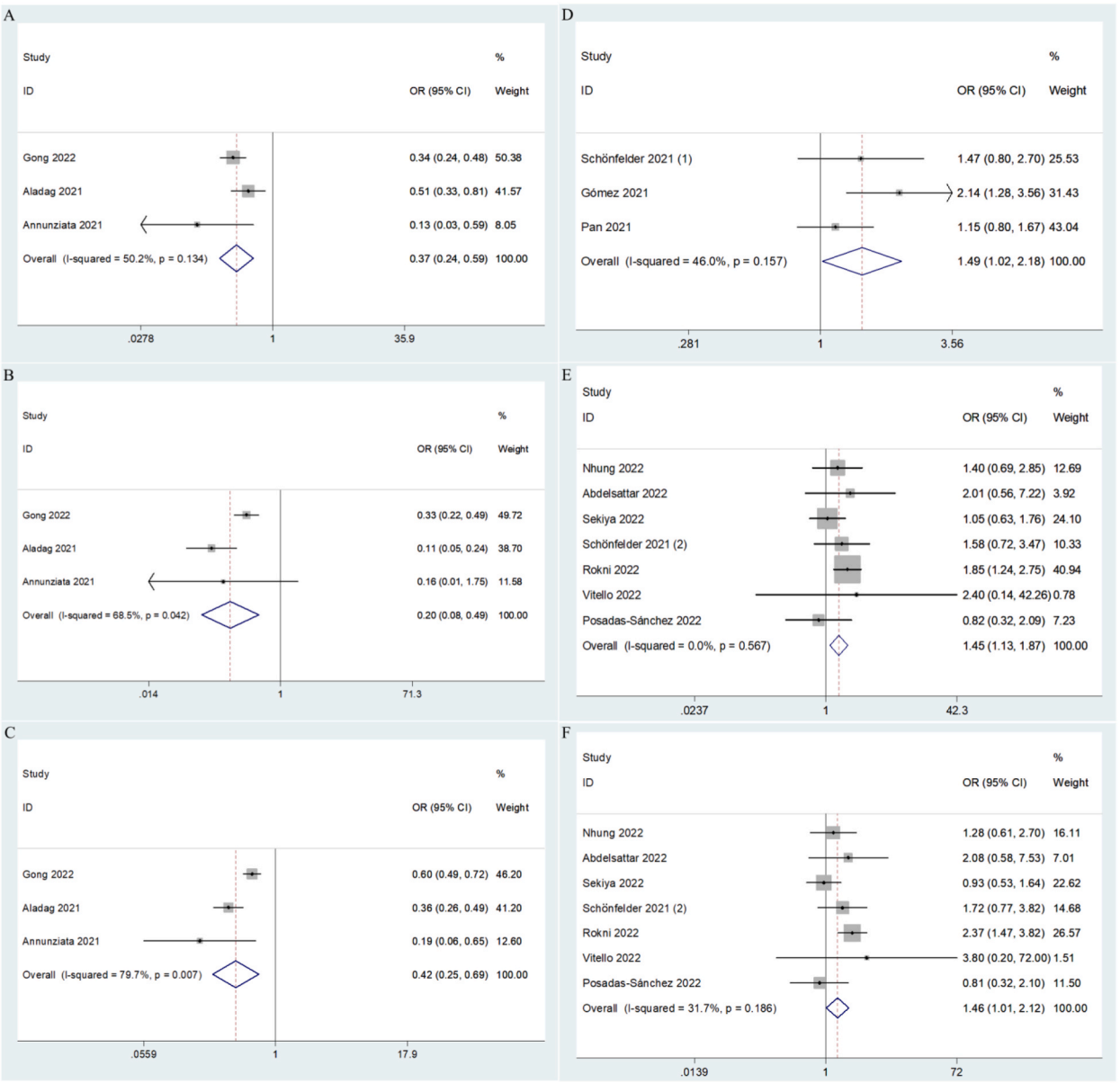

Fig. 2. Forest plot for the association between COVID-19 infection and significant genetic polymorphisms including *ACE* Ins/Del polymorphism in dominant (A), homozygote (B) and allelic (C) models; *IFITM3* rs12252 polymorphism in allelic model (D); *TMPRSS2* rs12329760 polymorphism in recessive (E) and homozygote models (F).

1.49, 95 % CI: 1.02–2.18, $P = 0.040$, Fig. 2D). And our results revealed a significant association between *TMPRSS2* rs12329760 polymorphism and an increased risk of COVID-19 infection in the recessive (AA vs. AG + GG, OR = 1.45, 95 % CI: 1.13–1.87, $P = 0.004$, Fig. 2E) and homozygote models (AA vs. GG, OR = 1.46, 95 % CI: 1.01–2.12, $P = 0.042$, Fig. 2F). However, there were no significant differences between COVID-19 infection and other genetic polymorphisms including *ACE1* rs1799752, *ACE1* rs4646994, *ACE2* rs2285666 and *VDR* rs2228570 under four genetic models (all $P > 0.05$). Meanwhile, subgroup analysis by ethnicity revealed that *ACE2* rs2285666 polymorphism was associated with a decreased risk of COVID-19 infection in Caucasian population under recessive (TT vs. TC + CC, OR = 0.56, 95 % CI: 0.40–0.79, $P = 0.001$), homozygote (TT vs. CC, OR = 0.52, 95 % CI: 0.30–0.89, $P = 0.018$) and allelic models (T vs. C, OR = 0.59, 95 % CI: 0.36–0.97, $P = 0.036$). Subgroup analysis of *TMPRSS2* rs12329760 polymorphism and COVID-19 infection by ethnicity also showed statistically significant results in Caucasian population under four genetic models (dominant model: AA + AG vs. GG, OR = 1.54, 95 % CI: 1.16–2.06, $P = 0.003$; recessive model: AA vs. AG + GG, OR = 1.80, 95 % CI: 1.27–2.56, $P = 0.001$; homozygote model: AA vs. GG, OR = 2.20, 95 % CI: 1.47–3.31, $P < 0.001$; allelic model: A vs. G, OR = 1.46, 95 % CI: 1.21–1.75, $P < 0.001$). In addition, subgroup analysis of *ACE1* rs4646994 polymorphism and COVID-19 infection by control groups indicated statistically significant results in healthy volunteers (recessive model: AA vs. AG + GG, OR = 0.59, 95 % CI:

0.41–0.84, $P = 0.003$; homozygote model: AA vs. GG, OR = 0.57, 95 % CI: 0.39–0.84, $P = 0.004$; allelic model: A vs. G, OR = 0.79, 95 % CI: 0.64–0.97, $P = 0.027$) and other groups (dominant model: AA + AG vs. GG, OR = 1.32, 95 % CI: 1.04–1.67, $P = 0.021$; recessive model: AA vs. AG + GG, OR = 1.30, 95 % CI: 1.03–1.64, $P = 0.026$; homozygote model: AA vs. GG, OR = 1.49, 95 % CI: 1.12–1.99, $P = 0.006$; allelic model: A vs. G, OR = 1.22, 95 % CI: 1.06–1.41, $P = 0.006$).

3.2.2. Genetic polymorphisms with COVID-19 severity

This meta-analysis showed the variant A allele of *ACE2* rs2074192 polymorphism might be related with significantly increased risk of COVID-19 severity in recessive (AA vs. AG + GG, OR = 3.38, 95 % CI: 1.47–7.78, $P = 0.004$, Supplemental Fig. 1A), homozygote (AA vs. GG, OR = 3.91, 95 % CI: 1.19–12.79, $P = 0.024$, Supplemental Fig. 1B) and allelic models (A vs. G, OR = 2.06, 95 % CI: 1.05–4.04, $P = 0.035$, Supplemental Fig. 1C). The *ACE2* rs2106809 polymorphism increased the risk of COVID-19 severity in recessive (CC vs. CT + TT, OR = 1.92, 95 % CI: 1.09–3.41, $P = 0.025$, Supplemental Fig. 1D), homozygote models (CC vs. TT, OR = 1.82, 95 % CI: 1.02–3.25, $P = 0.041$, Supplemental Fig. 1E). And the *IFITM3* rs12252 polymorphism was significantly associated with the risk of COVID-19 severity in recessive model (CC vs. CT + TT, OR = 3.06, 95 % CI: 1.35–6.94, $P = 0.008$, Supplemental Fig. 1F). The analysis of *TMPRSS2* rs2070788 indicated that a variant A allele decreased the risk of COVID-19 severity in recessive model (AA vs. AG + GG, OR = 0.60, 95 % CI: 0.39–0.93, $P = 0.023$, Supplemental Fig. 1G). The *VDR* rs1544410 polymorphism increased the risk of COVID-19 severity in homozygote model (TT vs. CC, OR = 1.56, 95 % CI: 1.03–2.36, $P = 0.038$, Supplemental Fig. 1H). However, there were no obvious differences between COVID-19 severity and other genetic polymorphisms including ACE Ins/Del, ACE1 rs1799752, ACE1 rs4646994, ACE2 rs2285666, IFNL3 rs12979860, IL6 rs1800795, IL6 rs1800797, TMPRSS2 rs12329760, TNFα rs1800629, VDR rs2228570, VDR rs731236 and VDR rs7975232 under four genetic models (all $P > 0.05$). Similarly, subgroup analysis by ethnicity revealed that *IFITM3* rs12252 polymorphism was associated with an increased risk of COVID-19 severity in Caucasian population under recessive (CC vs. CT + TT, OR = 4.85, 95 % CI: 1.44–16.34, $P = 0.011$), and homozygote models (CC vs. TT, OR = 5.37, 95 % CI: 1.29–22.34, $P = 0.021$).

3.2.3. Genetic polymorphisms with COVID-19 mortality

Our results indicated that the variant C allele of *IFITM3* rs12252 polymorphism might be related with significantly increased risk of COVID-19 mortality under all genetic models (dominant model: CC + CT vs. TT, OR = 2.75, 95 % CI: 1.26–6.00, $P = 0.011$, Figure Supplemental Fig. 2A; recessive mode: CC vs. CT + TT, OR = 6.46, 95 % CI: 4.60–9.08, $P = 0.001$, Supplemental Fig. 2B; homozygote model: CC vs. TT, OR = 7.86, 95 % CI: 4.36–14.19, $P = 0.001$, Supplemental Fig. 2C; allelic model: C vs. T, OR = 2.84, 95 % CI: 1.17–6.88, $P = 0.021$, Supplemental Fig. 2D). But we did not find any significant association between *TMPRSS2* rs12329760 polymorphism and COVID-19 mortality under four genetic models (all $P > 0.05$).

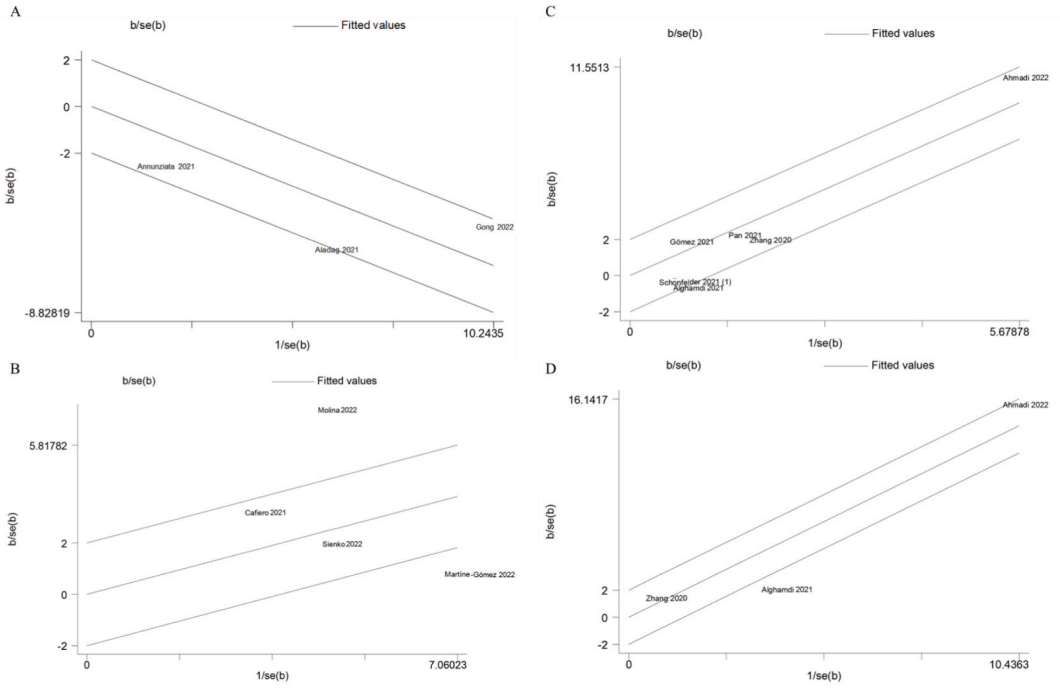

Fig. 3. Heterogeneity analysis for this meta-analysis including COVID-19 infection and *ACE* Ins/Del polymorphism in allelic model (A), COVID-19 severity and *ACE2* rs2074192 polymorphism under allelic model (B), COVID-19 severity and *IFITM3* rs12252 polymorphism under recessive model (C), COVID-19 mortality and *IFITM3* rs12252 polymorphism under allelic model (D).

3.3. Heterogeneity and sensitivity analyses

To detect the sources of obvious heterogeneity for four groups of significant genetic polymorphisms in this meta-analysis, Galbraith graph was performed. In detail, for the association of COVID-19 infection and *ACE* Ins/Del polymorphism under allelic model, the article studied by Gong et al. might be the main cause of heterogeneity (Fig. 3A). After removing this study, the heterogeneity of *ACE* Ins/Del polymorphism in allelic model decreased from 79.7 % to 0 %. As shown in Fig. 3B, the articles studied by Molina et al. and Martínez-Gómez et al. might be the main causes of heterogeneity for the relationship between COVID-19 severity and *ACE2* rs2074192 polymorphism under allelic model. For the association of COVID-19 severity and *IFITM3* rs12252 polymorphism under recessive model, the article studied by Ahmadi et al. might be the main cause of heterogeneity (Fig. 3C). After removing this study, the heterogeneity of *IFITM3* rs12252 polymorphism in recessive model decreased from 59.9 % to 23.1 %. Meanwhile, the article studied by Ahmadi et al. might also be the main cause of heterogeneity for the relationship between COVID-19 mortality and *IFITM3* rs12252 polymorphism under allelic model (Fig. 3D). Among the above four groups of significant genetic polymorphisms which were conducted to assess the sources of heterogeneity, sensitivity analyses were also performed to evaluate the stability of the results via sequential elimination of each study. As shown in Fig. 4A-D, there were no obvious changes of combined OR before and after the removal of each study in the above four groups, suggesting that our findings were stable and robust.

3.4. Publication bias

We performed the Begg's test and Egger's test to evaluate the publication bias across the included studies. As shown in Table 3, we observed no publication bias for the infection and mortality of COVID-19 with the significant genetic polymorphisms in this meta-analysis under all comparison models (all $P > 0.05$). For COVID-19 severity, there is no obvious evidence of publication bias by Begg's test under all four genetic models (all $P > 0.05$). The results of Egger's test for *ACE2* rs2106809 under allelic model ($t = -97.80$, $P = 0.007$) and *IFITM3* rs12252 under homozygote model ($t = -3.21$, $P = 0.033$) in the population of COVID-19 severity were represented by *P*-value <0.05 for the Egger's test, suggesting that further larger and higher-quality studies were still needed to demonstrate the finding. Publication bias of all genetic polymorphisms in this meta-analysis were available in Supplemental Table 5.

4. Discussion

There is mounting evidence that genetic variants may be related with the risk of specific infections, which can predict unfavorable disease outcomes, and provide more effective therapeutic interventions [73]. In recent years, a growing body of researches have

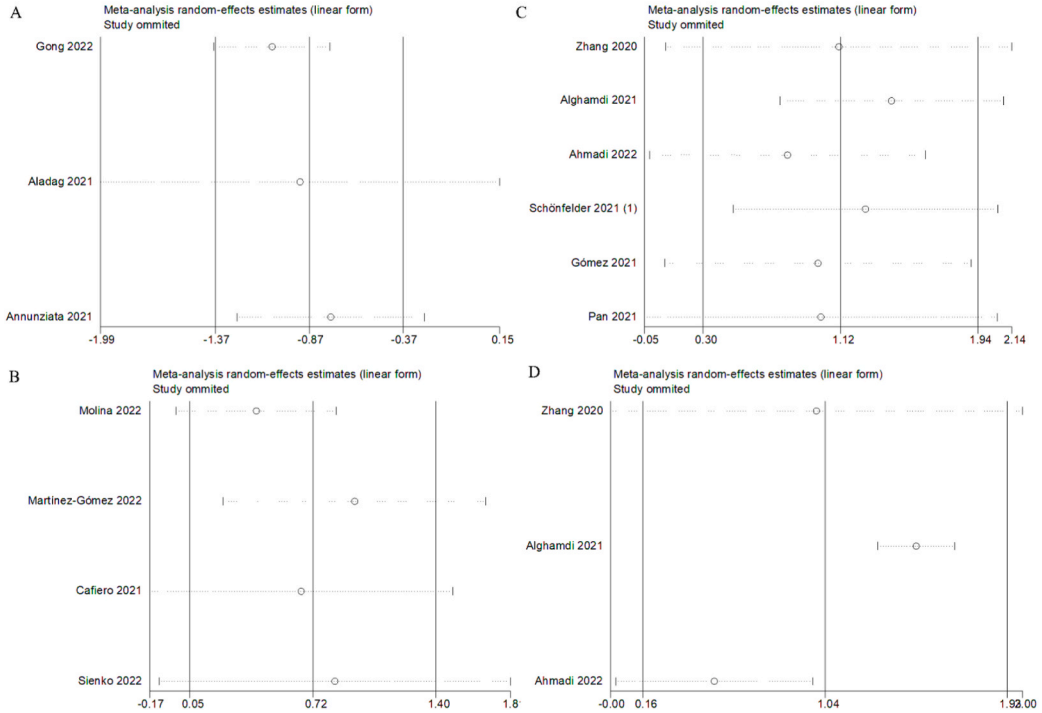

Fig. 4. Sensitivity analysis for this meta-analysis including COVID-19 infection and *ACE* Ins/Del polymorphism in allelic model (A), COVID-19 severity and *ACE2* rs2074192 polymorphism under allelic model (B), COVID-19 severity and *IFITM3* rs12252 polymorphism under recessive model (C), COVID-19 mortality and *IFITM3* rs12252 polymorphism under allelic model (D).

Table 3
Publication bias of significant genetic polymorphisms in this meta-analysis.

Group and genetic model	Begg's test		Egger's test	
	z value	*P* value	*t* value	*P* value
Infection *vs.* Non-infection				
ACE Ins/Del				
Dominant model	0	1.000	−0.59	0.662
Recessive model	0	1.000	−0.87	0.545
Homozygote model	0	1.000	−0.83	0.560
Allelic model	0	1.000	−1.37	0.401
IFITM3 rs12252				
Dominant model	0	1.000	−1.36	0.403
Recessive model	0	1.000	4.65	0.135
Homozygote model	0	1.000	4.62	0.136
Allelic model	0	1.000	0.89	0.535
TMPRSS2 rs12329760				
Dominant model	1.20	0.230	1.20	0.285
Recessive model	0.30	0.764	−0.24	0.816
Homozygote model	0.60	0.548	−0.06	0.953
Allelic model	0.90	0.368	0.75	0.486
Severe *vs.* Non-severe				
ACE2 rs2074192				
Dominant model	1.02	0.308	1.30	0.323
Recessive model	0.34	0.734	1.92	0.195
Homozygote model	1.02	0.308	1.74	0.224
Allelic model	1.02	0.308	1.25	0.337
ACE2 rs2106809				
Dominant model	1.04	0.296	−4.37	0.143
Recessive model	0	1.000	−1.07	0.480
Homozygote model	1.04	0.296	−1.86	0.313
Allelic model	1.04	0.296	−97.80	0.007
IFITM3 rs12252				
Dominant model	0	1.000	−1.26	0.275
Recessive model	0.75	0.452	−2.69	0.055
Homozygote model	0	1.000	−3.21	0.033
Allelic model	0.75	0.452	−1.46	0.218
TMPRSS2 rs2070788				
Dominant model	0	1.000	−1.18	0.447
Recessive model	0	1.000	−0.47	0.719
Homozygote model	0	1.000	−0.90	0.532
Allelic model	0	1.000	−1.16	0.452
VDR rs1544410				
Dominant model	1.04	0.296	3.91	0.159
Recessive model	0	1.000	0.18	0.884
Homozygote model	0	1.000	2.46	0.245
Allelic model	0	1.000	1.74	0.332
Deceased *vs.* Survived				
IFITM3 rs12252				
Dominant model	0	1.000	−0.78	0.579
Recessive model	1.04	0.296	−2.16	0.276
Homozygote model	0	1.000	−3.25	0.190
Allelic model	0	1.000	−0.66	0.630

Annotation: ACE: angiotensin-converting enzyme type; IFITM3: interferon-induced transmembrane protein 3; TMPRSS2: transmembrane serine protease type 2; VDR: vitamin D receptor.

revealed that COVID-19 disease is closely related to genetic variants in renin-angiotensin-aldosterone system (*ACE1*, *ACE2*) [26], cytokines (*IL6*, *TNFα*) [45], type I interferon-related genes (*IFITM3*, *IFNL3*) [65], the ABO blood group system and the human leukocyte antigen (HLA) [74]. However, the associations between genetic polymorphisms with infection and outcomes of COVID-19 remain partially controversial. With the publication of new high-quality and well-designed studies, an updated meta-analysis is required to confirm the roles of genetic polymorphisms in COVID-19 disease. Although several meta-analyses analyzed the relationship between specific gene polymorphisms with a certain risk of COVID-19 [11,75], the present data aimed to provide a more comprehensive estimate on three aspects of researches including the relationship between all genetic polymorphisms and the infection, severity and mortality of COVID-19, rather than one of them.

In this meta-analysis, a total of 62 studies with 19600 cases and 28899 controls was included. Firstly, 28 records with 8296 cases and 8822 controls were included to assess the association between COVID-19 infection and genetic polymorphisms. The analysis of *ACE* Ins/Del polymorphism might significantly decrease the risk of COVID-19 infection under dominant, homozygote and allelic models. Meanwhile, the *IFITM3* rs12252 and *TMPRSS2* rs12329760 polymorphisms significantly increased the risk of COVID-19 infection under one or more models. Secondly, the analysis of ACE2 rs2074192, ACE2 rs2106809 and VDR rs1544410

polymorphisms might be related with significantly increased risk of COVID-19 severity in one or more models. Moreover, IFITMS rs12252 and TMPRSS2 rs2070788 polymorphisms showed significant associations with COVID-19 severity in recessive model, but not in other models, which might be related to heterogeneity of the included literatures. Finally, the variant C allele of *IFITM3* rs12252 polymorphism might be associated with obvious increased risk of COVID-19 mortality under all genetic models. In addition, most of the included studies were detected to be of good quality with an acceptable risk of bias.

The above genes (*ACE, TMPRSS2, IFITM3, VDR*) that we analyzed play important roles in the development of COVID-19. SARS-CoV-2 belonging to coronavirus is highly selective binding the ACE2-expressing cells, which is widely distributed in blood vessels, tissues and organs including lungs, heart, kidney and eye, contributing to the widespreading of SARS-CoV-2 in humans [76]. There is evidence that TMPRSS2 interacts with the spike protein of SARS-CoV-2 to allow the fusion with host-membrane and endocytosis [77]. *IFITM3* encoded the interferon-induced transmembrane proteins play a critical role in the antiviral defense in the adaptive and innate immune response. The variants of *IFITM3* gene are known risk factor for severe viral diseases including SARS-CoV [78]. Moreover, genetic variations in the *VDR* gene can influence the activity, stability and expression levels of VDR products. And the deficiency and insufficiency of Vitamin D (VD) further lead to many pathogenic outcomes, including respiratory infections [79].

Our findings had some limitations which should be considered. Some genetic polymorphisms just reported in one or two articles are not included in this meta-analysis. Another limitation is the occurrence of heterogeneity between some studies, which may be related to the ethnicity and study quality. Meanwhile, there are very few results in the absence of publication bias. In addition, it has been reported that certain comorbidities are known risk factors for COVID-19 severity and mortality [80]. Our study did not address the possible impact of comorbidities on the relationship between genetic polymorphisms and COVID-19 severity and mortality, due to the small amounts of studies. Given these limitations, our results should be further assessed by the larger, better-designed studies.

In conclusion, this study provides an overview for the role of genetic polymorphisms in COVID-19 disease. Polymorphisms in ACE Ins/Del, ACE2 rs2074192, ACE2 rs2106809, IFITM3 rs12252, TMPRSS2 rs2070788, TMPRSS2 rs12329760, and VDR rs1544410 influence the infection, severity or mortality of COVID-19. Our findings may provide more extensive and indepth strategies to reveal the pathogenesis of COVID-19.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Hongyue Ren: Writing – original draft, Software, Funding acquisition, Formal analysis, Data curation. **Yanyan Lin:** Methodology, Data curation. **Lifeng Huang:** Methodology, Formal analysis. **Wenxin Xu:** Software, Methodology. **Deqing Luo:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis. **Chunbin Zhang:** Writing – review & editing, Methodology, Funding acquisition.

Declaration of competing interest

The author (s) declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23662.

References

[1] R. Chilamakuri, S. Agarwal, COVID-19: characteristics and therapeutics, Cells 10 (2) (2021).
[2] Y. Shi, et al., An overview of COVID-19, J. Zhejiang Univ. - Sci. B 21 (5) (2020) 343–360.
[3] Z. Wu, J.M. McGoogan, Characteristics of and important oessons from the coronavirus disease 2019 (COVID-19) sutbreak in China: pummary of a report of 72 314 cases from the Chinese center for disease control and frevention, JAMA 323 (13) (2020) 1239–1242.

[4] J.M. Jin, et al., Gender differences in patients with COVID-19: rocus on severity and mortality, Front. Public Health 8 (2020) 152.
[5] A. Abobaker, et al., The impact of certain genetic variants (single nucleotide polymorphisms) on incidence and severity of COVID-19, J. Gene Med. 23 (2) (2021), e3310.
[6] S. Abdelsattar, et al., ACE2 and TMPRSS2 SNPs as determinants of susceptibility to, and severity of, a COVID-19 infection, Br. J. Biomed. Sci. 79 (2022), 10238.
[7] G.A. Vitello, et al., Allelic variations in the human genes TMPRSS2 and CCR5, and the Resistance to viral infection by SARS-CoV-2, Int. J. Mol. Sci. 23 (16) (2022).
[8] T. Sekiya, et al., TMPRSS2 gene polymorphism common in East Asians confers decreased COVID-19 susceptibility, Front. Microbiol. 13 (2022), 943877.
[9] R. Posadas-Sanchez, et al., Association of the transmembrane serine protease-2 (TMPRSS2) polymorphisms with COVID-19, Vasc. Pharmacol. 14 (9) (2022).
[10] C. Dieter, et al., Genetic polymorphisms associated with susceptibility to COVID-19 disease and severity: a systematic review and meta-analysis, PLoS One 17 (7) (2022), e0270627.
[11] W. Saengsiwaritt, et al., Genetic polymorphisms of ACE1, ACE2, and TMPRSS2 associated with COVID-19 severity: a systematic review with meta-analysis, Rev. Med. Virol. 32 (4) (2022), e2323.
[12] H.N. Ali, et al., Association of tumor necrosis factor alpha -308 single nucleotide polymorphism with SARS CoV-2 infection in an Iraqi Kurdish population, J. Clin. Lab. Anal. 36 (5) (2022), e24400.
[13] A. Jafarpoor, et al., VDR gene polymorphisms are associated with the increased susceptibility to COVID-19 among iranian population: a case-control study, Int. J. Immunogenet. 49 (4) (2022) 243–253.
[14] M. Akbari, et al., Assessment of ACE1 variants and ACE1/ACE2 expression in COVID-19 patients, Vascul Pharmacol 142 (2022), 106934.
[15] I. Ahmadi, et al., Impact of interferon-induced transmembrane protein 3 gene rs12252 polymorphism on COVID-19 mortality, Cytokine 157 (2022), 155957.
[16] K. Knobloch, et al., Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias, J. Cranio-Maxillo-Fac. Surg. 39 (2) (2011) 91–92.
[17] W.H. Organization, Clinical Management of COVID-19: Living Guideline, 23 June 2022, 2022.
[18] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (9) (2010) 603–605.
[19] H. Abbaszadeh, et al., Angiotensin-converting enzyme 1 and voltage-gated potassium channel-interacting protein 4 gene polymorphisms in COVID-19 patients from east of Iran, Clin. Chim. Acta 536 (2022) 39–44.
[20] R. Abdollahzadeh, et al., Association of Vitamin D receptor gene polymorphisms and clinical/severe outcomes of COVID-19 patients, Infect. Genet. Evol. 96 (2021), 105098.
[21] S.H.A. Agwa, et al., Association between interferon-lambda-3 rs12979860, TLL1 rs17047200 and DDR1 rs4618569 variant polymorphisms with the course and outcome of SARS-CoV-2 patients, Genes 12 (6) (2021).
[22] E. Aladag, et al., Human cce D/I polymorphism could affect the Clinicobiological course of COVID-19, J Renin Angiotensin Aldosterone Syst 2021 (2021), 5509280.
[23] S.A. Aladawy, et al., Polymorphism in promotor region of IL6 gene as a predictor for severity in COVID -19 patients, Egypt, J. Immunol. 29 (2) (2022) 1–9.
[24] F. Al-Anouti, et al., Associations between genetic variants in the vitamin D petabolism rathway and severity of COVID-19 among UAE lesidents, Nutrients 13 (11) (2021).
[25] J. Alghamdi, et al., Interferon-induced transmembrane protein-3 genetic variant rs12252 is associated with COVID-19 mortality, Genomics 113 (4) (2021) 1733–1741.
[26] N. Alimoradi, et al., SNPs of ACE1 (rs4343) and ACE2 (rs2285666) genes are linked to SARS-CoV-2 infection but not with the severity of disease, Virol. J. 19 (1) (2022) 48.
[27] E. Amodio, et al., SARS-CoV-2 viral ooad, IFN lambda polymorphisms and the course of COVID-19: an ibservational study, J. Clin. Med. 9 (10) (2020).
[28] M. Angulo-Aguado, et al., Association between the LZTFL1 rs11385942 polymorphism and COVID-19 severity in Colombian population, Front. Med. 9 (2022), 910098.
[29] A. Annunziata, et al., The angiotensin converting enzyme deletion/deletion genotype is a risk factor for severe COVID-19: umplication and atility for patients edmitted to dmergency Department, Medicina-Lithuania 57 (8) (2021).
[30] T. Apaydin, et al., Effects of vitamin D receptor gene polymorphisms on the prognosis of COVID-19, Clin. Endocrinol. 96 (6) (2022) 819–830.
[31] M.G. Balzanelli, et al., Analysis of gene single nucleotide polymorphisms in COVID-19 disease sighlighting the susceptibility and the severity towards the infection, Diagnostics 12 (11) (2022).
[32] S. Baştuğ, et al., Are angiotensin converting enzyme (ACE1/ACE2) gene variants associated with the clinical severity of COVID-19 pneumonia? A single-center cohort study, Anatol. J. Cardiol. 26 (2) (2022) 133–140.
[33] S.S. Beheshti Shirazi, et al., rs12329760 polymorphism in transmembrane serine protease 2 gene and risk of coronavirus disease 2019 mortality, BioMed Res. Int. 2022 (2022), 7841969.
[34] C. Cafiero, et al., Angiotensin system polymorphisms' in SARS-CoV-2 positive patients: assessment between iymptomatic and asymptomatic patients: a pilot study, Pharmacogenomics Personalized Med. 14 (2021) 621–629.
[35] C.C. de Andrade, et al., A polymorphism in the TMPRSS2 gene dncreases the risk of heath in older patients rospitalized with COVID-19, Viruses 14 (11) (2022).
[36] S. Falahi, et al., Evaluation of the relationship between IL-6 gene single nucleotide polymorphisms and the severity of COVID-19 in an Iranian population, Cytokine 154 (2022), 155889.
[37] A. Faridzadeh, et al., The role of ACE1 I/D and ACE2 polymorphism in the outcome of Iranian COVID-19 patients: a case-control study, Front. Genet. 13 (2022).
[38] J. Gómez, et al., The Interferon-induced transmembrane protein 3 gene (IFITM3) rs12252 C variant is associated with COVID-19, Cytokine 137 (2021), 155354.
[39] J. Gómez, et al., Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome, Gene 762 (2020), 145102.
[40] P. Gong, et al., Angiotensin-converting enzyme genotype-specific immune cesponse nontributes to the susceptibility of COVID-19: a rested case-control study, Front. Pharmacol. 12 (2021), 759587.
[41] O. Gunal, et al., Angiotensin-converting enzyme-1 gene insertion/deletion polymorphism may be associated with COVID-19 clinical severity: a prospective cohort study, Ann. Saudi Med. 41 (3) (2021) 141–146.
[42] J.A. Hubacek, et al., ACE I/D polymorphism in Czech first-wave SARS-CoV-2-positive survivors, Clin. Chim. Acta 519 (2021) 206–209.
[43] K. Jevnikar, et al., The role of ACE, ACE2, and AGTR2 polymorphisms in COVID-19 severity and the presence of COVID-19-related detinopathy, Genes 13 (7) (2022).
[44] S. Karakaş Çelik, et al., Polymorphisms of ACE (I/D) and ACE2 receptor gene (Rs2106809, Rs2285666) are not related to the clinical course of COVID-19: a case study, J. Med. Virol. 93 (10) (2021) 5947–5952.
[45] F. Kerget, B. Kerget, Frequency of interleukin-6 rs1800795 (-174G/C) and rs1800797 (-597G/A) polymorphisms in COVID-19 patients in Turkey who mevelop aacrophage zctivation syndrome, Jpn. J. Infect. Dis. 74 (6) (2021) 543–548.
[46] F. Khalilzadeh, et al., Angiotensin-converting enzyme 2 rs2285666 polymorphism and clinical parameters as the determinants of COVID-19 severity in Iranian population, Int. J. Immunogenet. 49 (5) (2022) 325–332.
[47] N. Kotur, et al., Association of vitamin D, sinc and helenium related genetic variants with COVID-19 disease severity, Front. Nutr. 8 (2021).
[48] I. Lapić, et al., Association of polymorphisms in genes encoding prothrombotic and cardiovascular risk factors with disease severity in COVID-19 patients: a pilot study, J. Med. Virol. 94 (8) (2022) 3669–3675.
[49] N.Z. Mahdi, et al., Assessing the potential correlation of polymorphisms in the TMPRSS2 gene with severity of COVID 19 patients, Biomedicine 42 (5) (2022) 1034–1039.
[50] L.E. Martínez-Gómez, et al., ACE and ACE2 gene variants are associated with severe outcomes of COVID-19 in men, Front. Immunol. 13 (2022), 812940.
[51] M.M. Mir, et al., Strong association of angiotensin converting enzyme-2 gene insertion/deletion polymorphism with susceptibility to SARS-CoV-2, aypertension, coronary Artery disease and COVID-19 disease mortality, Pharmacogenetics Genom. 11 (11) (2021).

[52] B. Mohlendick, et al., ACE2 polymorphism and susceptibility for SARS-CoV-2 infection and severity of COVID-19, Mol. Genet. Genom. 31 (8) (2021) 165–171.
[53] M. Najafi, M.R. Mahdavi, Association investigations between ACE1 and ACE2 polymorphisms and severity of COVID-19 disease, Mol Genet Genomics (2022) 1–10.
[54] V.P. Nhung, et al., Host genetic risk factors associated with COVID-19 susceptibility and severity in Vietnamese, Genes 13 (10) (2022).
[55] Y. Pan, et al., Association between rs12252 polymorphism in IFITM3 gene and COVID-19, Int. J. Virol. 28 (3) (2021) 192–195.
[56] A. Papadopoulou, et al., Angiotensin-converting-enzyme insertion/deletion polymorphism, ACE activity, and COVID-19: a rather controversial hypothesis. A case-control study, J. Med. Virol. 94 (3) (2022) 1050–1059.
[57] E.M. Peralta, et al., TaqI polymorphism of the VDR gene: aspects related to the clinical behavior of COVID-19 in Cuban patients, Egyptian Journal of Medical Human Genetics 22 (1) (2021).
[58] P. Rahimi, et al., The association between interferon lambda 3 and 4 gene single-nucleotide polymorphisms and the recovery of COVID-19 patients, Virol. J. 18 (1) (2021) 221.
[59] Reviono, et al., Frequency of Interleukin-6 rs 1800796 (-572G/C) TNF-? rs1800750 (-376G/A), and 1800629 (-308G/A) polymorphism in COVID-19 patients with clinical degrees in Central Java, Bali Med. J. 11 (3) (2022) 1364–1368.
[60] M. Rokni, et al., Association of TMPRSS2 gene polymorphisms with COVID-19 severity and mortality: a case-control study with pomputational analyses, Appl. Biochem. Biotechnol. 194 (8) (2022) 3507–3526.
[61] H. Saad, et al., The role of angiotensin converting enzyme 1 insertion/deletion genetic polymorphism in the risk and severity of COVID-19 infection, Front. Med. 8 (2021), 798571.
[62] M. Sabater Molina, et al., Polymorphisms in ACE, ACE2, AGTR1 genes and severity of COVID-19 disease, PLoS One 17 (2) (2022), e0263140.
[63] A. Saleh, et al., Association of TNF-alpha G-308 a oromoter polymorphism with the course and outcome of COVID-19 patients, Immunol. Invest. 51 (3) (2022) 546–557.
[64] K. Schoenfelder, et al., Transmembrane serine protease 2 polymorphisms and susceptibility to severe acute respiratory syndrome coronavirus type 2 infection: a German case-control study, Front. Genet. 12 (2021).
[65] K. Schönfelder, et al., The influence of IFITM3 polymorphisms on susceptibility to SARS-CoV-2 infection and severity of COVID-19, Cytokine 142 (2021), 155492.
[66] J. Sienko, et al., Association of ACE2 gene variants with the severity of COVID-19 disease-A prospective Observational study, Int J Environ Res Public Health 19 (19) (2022).
[67] F. Sotomayor-Lugo, et al., The role of tumor necrosis factor alpha-308A > G polymorphism on the clinical states of SARS-CoV-2 infection, Hum. Genom. 23 (1) (2022).
[68] S. Verma, et al., Impact of I/D polymorphism of angiotensin-converting enzyme 1 (ACE1) gene on the severity of COVID-19 patients, Infect. Genet. Evol. 91 (2021), 104801.
[69] S. Verma, et al., Genetic polymorphisms of IL6 gene -174G > C and -597G > A are associated with the risk of COVID-19 severity, Int. J. Immunogenet. 50 (1) (2023) 5–11.
[70] L. Wulandari, et al., Initial study on TMPRSS2 p.Val160Met genetic variant in COVID-19 patients, Hum Genomics 15 (1) (2021) 29.
[71] N.M.S. Zeidan, et al., Vitamin D deficiency and vitamin D receptor FokI polymorphism as risk factors for COVID-19, Pediatr. Res.
[72] Y. Zhang, et al., Interferon-induced transmembrane protein 3 genetic variant rs12252-C associated with disease severity in coronavirus disease 2019, J. Infect. Dis. 222 (1) (2020) 34–37.
[73] S.A.R. Mortazavi-Tabatabaei, et al., Pattern of rntibacterial uesistance in trinary Tract infections: a systematic review and meta-analysis, Int. J. Prev. Med. 10 (2019) 169.
[74] A. Amoroso, et al., HLA and AB0 polymorphisms may influence SARS-CoV-2 infection and COVID-19 severity, Transplantation 105 (1) (2021) 193–200.
[75] Z. Dobrijevic, et al., The association of ACE1, ACE2, TMPRSS2, IFITM3 and VDR polymorphisms with COVID-19 severity: a systematic review and meta-analysis, Excli j 21 (2022) 818–839.
[76] S.R. Tipnis, et al., A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase, J. Biol. Chem. 275 (43) (2000) 33238–33243.
[77] J. Shang, et al., Cell entry mechanisms of SARS-CoV-2, Proc Natl Acad Sci U S A 117 (21) (2020) 11727–11734.
[78] M.S. Diamond, M. Farzan, The broad-spectrum antiviral functions of IFIT and IFITM proteins, Nat. Rev. Immunol. 13 (1) (2013) 46–57.
[79] D.O. Meltzer, et al., Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence, medRxiv, 2020.
[80] I. Djaharuddin, et al., Comorbidities and mortality in COVID-19 patients, Gac. Sanit. 35 (Suppl 2) (2021) S530–s532.