Received: 6 December 2021 | Revised: 27 February 2022 | Accepted: 6 September 2022

DOI: 10.1002/mgg3.2063

Molecular Genetics & Genomic Medicine Open Access WILEY

REVIEW ARTICLE

Association of *ACE1* I/D rs1799752 and *ACE2* rs2285666 polymorphisms with the infection and severity of COVID-19: A meta-analysis

Md. Abdul Aziz[1,2] | **Mohammad Safiqul Islam**[2,3]

[1]Department of Pharmacy, Faculty of Pharmacy and Health Sciences, State University of Bangladesh, Dhaka, Bangladesh

[2]Laboratory of Pharmacogenomics and Molecular Biology, Department of Pharmacy, Noakhali Science and Technology University, Sonapur, Bangladesh

[3]Department of Pharmacy, Faculty of Science, Noakhali Science and Technology University, Sonapur, Bangladesh

Correspondence
Mohammad Safiqul Islam, Department of Pharmacy, Noakhali Science and Technology University, Noakhali-3814, Bangladesh.
Email: research_safiq@nstu.edu.bd; research_safiq@yahoo.com

Abstract

Background: *ACE1* I/D rs1799752 and *ACE2* rs2285666 genetic polymorphisms could play a critical role in altering the clinical outcomes of SARS-CoV-2. The findings of previous studies remained inconclusive. This meta-analysis was performed to evaluate the association and provide a more reliable outcome.

Methods: This study was completed following the updated recommendations of PRISMA using RevMan 5.4.1 statistical software.

Results: A total of 11 studies with 950 severe cases and 1573 non-severe cases with COVID-19 infection were included. Pooled analysis showed that *ACE1* I/D polymorphism was correlated with the severity of SARS-CoV-2 in the DD genotype and D allele for the fixed-effects model (OR:1.27 and OR:1.17). Besides, codominant 3, recessive, and allele models were associated with the severity of the fixed-effects model (OR:1.35, OR:1.37, and OR:1.20) in Caucasian ethnicity. *ACE2* rs2285666 was linked with the severity in codominant 3 (OR:2.63, for both random- and fixed effects-models), overdominant (OR:1.97, for random-effects model and OR:1.97, for fixed effects-model), and recessive model (OR:0.41 for fixed- and random-effects model). Allele model of rs2285666 showed a significant association in the fixed-effects model (OR:1.61).

Conclusion: Our present meta-analysis suggests that *ACE1* I/D rs1799752 and *ACE2* rs2285666 variants may enhance the severity in SARS-CoV-2 infected patients. Future studies are warranted to verify our findings.

KEYWORDS

ACE1, *ACE2*, COVID-19, meta-analysis, SARS-CoV-2

1 | INTRODUCTION

The emergence of COVID-19 pandemic, which occurred by the novel coronavirus SARS-CoV-2, is contemplated to be one of the most severe threats to humankind of the century due to its higher morbidity and mortality rate (Huang et al., 2020; Yamamoto et al., 2021; Zhu et al., 2020). The SARS-CoV-2 virus enters the host cell

via the angiotensin-converting enzyme 2 (ACE2) receptor. The viral spike glycoprotein interacts with the ACE2 receptor that helps to release viral RNA into the cytoplasm, establishing subsequent infection and inflammation in the lungs and other organs. Angiotensin-converting enzyme 1 (ACE1), on the contrary, plays a reciprocal role to that of ACE2. It modulates the expression of ACE2 via regulating angiotensin II levels (Hoffmann et al., 2020; Livshits et al., 2021; Parit & Jayavel, 2021; Peng et al., 2021).

A commonly investigated gene during the COVID-19 pandemic is the angiotensin-converting enzyme 1 (*ACE1*), found on the chromosomal location 17q23.3. It comprises an insertion or a deletion (I/D) allele that forms II, ID, and DD genotypes (Rigat et al., 1990). Studies have previously reported the association between *ACE1* (OMIM 106180) I/D (rs1799752) polymorphism and hypertension, hypertrophic cardiomyopathy, obesity, and myocardial infarction, which are notable comorbidities leading to the severity of COVID-19 (Gemmati et al., 2020; Lin et al., 2019; Yoo et al., 2017; Yuan et al., 2017). The *ACE1* rs1799752 has been investigated extensively during the post-COVID-19 situation to correlate with the susceptibility of SARS-CoV-2 infection, associated clinical outcomes, and mortality rate (Çelik et al., 2021; Delanghe et al., 2020; Gómez et al., 2020; Hatami et al., 2020; Pati et al., 2020; Saadat, 2020; Yamamoto et al., 2020). However, these studies reported inconsistent outcomes, which should be investigated more comprehensively (Gómez et al., 2020; Yamamoto et al., 2021).

Recent studies have demonstrated that single-nucleotide polymorphisms (SNPs) in *ACE2* (OMIM 300335) could play a critical role in altering the susceptibility and clinical outcomes of SARS-CoV-2 by modifying the level of expression and binding affinity (Cao et al., 2020; Çelik et al., 2021; Darbani, 2020; Devaux et al., 2020; Gemmati et al., 2020; Gómez et al., 2020; Hou et al., 2020; Li, Zhou, et al., 2020; Möhlendick et al., 2021; Novelli et al., 2020). SNP rs2285666, one of the most frequently investigated polymorphisms in *ACE2*, is located in the splice site of intron 3 found to be associated with severities of SARS-CoV-2 (Cafiero et al., 2021; Gómez et al., 2020; Möhlendick et al., 2021). As of the previous line of evidence, cerebral stroke, coronary heart disease (CHD), diabetes, and hypertension are correlated with

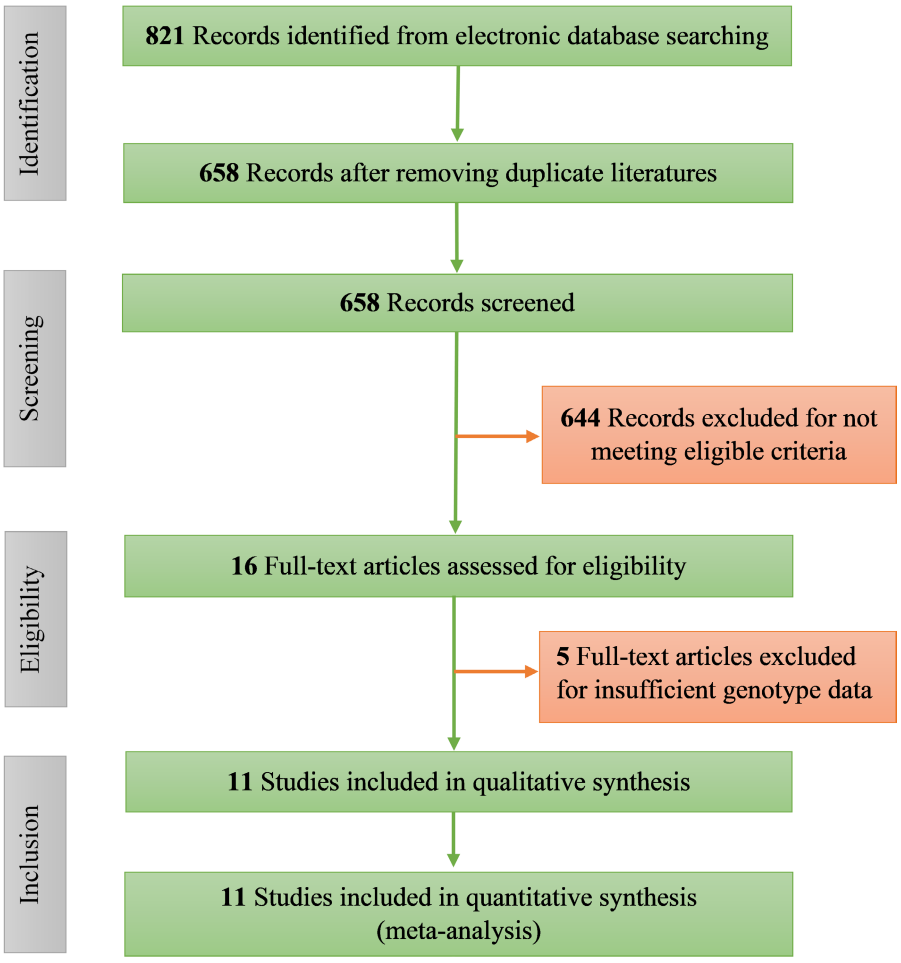

FIGURE 1 PRISMA flow chart showing the process of study identification and selection.

TABLE 1 Characteristics of the studies included in the meta-analysis

Study ID	Year	Country	Ethnicity	Severe cases	Non-severe cases	DD	DI	II	DD	DI	II	HWE *p*-value
ACE1 I/D rs1799752												
Akbari et al.	2021	Iran	Asian	37	54	6	31	0	11	39	4	.001
Aladag et al.	2021	Turkey	Caucasian	12	53	2	10	0	23	22	8	.478
Cafiero et al.	2021	Italy	Caucasian	54	50	32	15	7	7	21	22	.587
Calabrese et al.	2021	Italy	Caucasian	25	43	18	4	3	20	21	2	.227
Çelik et al.	2021	Turkey	Caucasian	35	119	14	15	6	34	64	21	.334
Gomez et al.	2020	Spain	Caucasian	67	137	31	31	5	44	76	17	.071
Gunal et al.	2021	Turkey	Caucasian	30	60	19	2	9	26	12	22	0
Hubacek et al.	2021	Czech Republic	Caucasian	245	163	51	123	71	40	87	36	.384
Mir et al.	2021	Saudi Arabia	Asian	43	74	12	20	11	45	24	5	.472
Möhlendick et al.	2021	Germany	Caucasian	90	207	31	40	19	74	86	47	.026
Verma et al.	2021	India	Asian	120	149	30	48	42	17	58	74	.283
Total				758	1109	246	339	173	341	510	258	

Study ID	Year	Country	Ethnicity	Severe cases	Non-severe cases	GG	GA	AA	GG	GA	AA	HWE *p-value*
ACE2 rs2285666												
Çelik et al.	2021	Turkey	Caucasian	35	120	5	6	24	23	27	70	<.001
Gomez et al.	2020	Spain	Caucasian	67	137	12	3	52	18	25	94	<.001
Möhlendick et al.	2021	Germany	Caucasian	90	207	4	6	80	23	34	150	<.001
Total				192	464	21	15	156	64	86	314	

TABLE 2 Meta-analysis of the association of *ACE1* I/D rs1799752 polymorphism with the infection and severity of COVID-19

Genetic models (*ACE1* I/D rs1799752)	Test of heterogeneity		Test of association					
			Random-effects model			Fixed-effects model		
	p-value	I^2 (%)	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Overall population								
DI vs. II	.065	42.64	1.00	0.66–1.50	.984	1.00	0.77–1.31	.985
DD vs. II	<.0001	77.84	1.46	0.73–2.91	.285	1.32	0.99–1.77	.059
DD vs. DI	<.0001	74.00	1.34	0.81–2.22	.249	1.24	0.98–1.57	.077
DD + DI vs. II	.0007	67.29	1.22	0.74–1.99	.436	1.16	0.91–1.49	.218
DD vs. DI + II	<.0001	80.32	1.35	0.80–2.27	.263	1.27	1.02–1.59	**.031**
DI vs. DD + II	.0086	57.71	0.90	0.64–1.27	.559	0.92	0.75–1.12	.397
D vs. I	<.0001	83.90	1.24	0.86–1.80	.251	1.17	1.02–1.35	**.025**
Caucasian								
DI vs. II	.134	37.01	0.96	0.60–1.53	.860	0.92	0.67–1.26	.605
DD vs. II	.001	71.20	1.65	0.82–3.30	.161	1.28	0.92–1.79	.144
DD vs. DI	.0006	72.44	1.64	0.92–2.91	.092	1.35	1.03–1.78	**.029**
DD + DI vs. II	.0165	59.15	1.30	0.77–2.19	.328	1.10	0.82–1.46	.537
DD vs. DI + II	.0001	76.38	1.62	0.93–2.81	.086	1.37	1.07–1.76	**.012**
DI vs. DD + II	.0167	59.08	0.74	0.49–1.13	.163	0.80	0.63–1.02	.068
D vs. I	<.0001	80.10	1.42	0.95–2.12	.088	1.20	1.02–1.41	**.031**
Asian								
DI vs. II	.068	62.79	1.10	0.33–3.66	.877	1.23	0.76–1.99	.410
DD vs. II	<.0001	90.32	1.08	0.09–1.65	.951	1.47	0.81–2.68	.209
DD vs. DI	.003	82.38	0.80	0.24–2.68	.713	0.93	0.57–1.52	.772
DD + DI vs. II	.002	84.42	1.06	0.18–6.32	.951	1.35	0.86–2.11	.189
DD vs. DI + II	.0001	89.79	0.80	0.17–3.63	.772	0.98	0.62–1.56	.931
DI vs. DD + II	.354	3.76	1.32	0.88–1.96	.175	1.31	0.89–1.92	.174
D vs. I	<.0001	92.51	0.86	0.30–2.48	.783	1.11	0.85–1.45	.445

Bold *p*-values indicate statistically significant.

rs2285666 polymorphism, the comorbidities which lead to the worse clinical outcome in COVID-19 patients (Chen et al., 2021; Möhlendick et al., 2021; Pinheiro et al., 2019; Wu et al., 2017; Yang et al., 2015). A study by Celik and others (Çelik et al., 2021) failed to demonstrate any association between this SNP and severe outcomes of COVID-19.

Given that *ACE1* and *ACE2* polymorphisms may be correlated with the infection and severity of COVID-19, the present meta-analysis aimed to systematically evaluate and validate the association of both *ACE1* I/D rs1799752 and *ACE2* rs2285666 genetic polymorphisms with SARS-CoV-2-infected patients based on the available data.

2 | METHODS AND MATERIALS

This meta-analysis was performed following the updated recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Page et al., 2021).

2.1 | Literature search

Two authors (MAA and MSI) systematically searched electronic databases, including PubMed, Web of Science, Cochrane Library, EMBASE, Science Direct, and Google Scholar for eligible published pieces of literature through November 2021, using the following terms: COVID-19, SARS-CoV-2, coronavirus, angiotensin-converting enzyme, *ACE*, *ACE1* I/D, *ACE1* insertion–deletion, *ACE2*, rs1799752, rs2285666, polymorphism, and variants either as a sole form or in combination. To retrieve all available literature, the authors also checked the references from related studies. All the studies were selected independently by the authors and disagreements

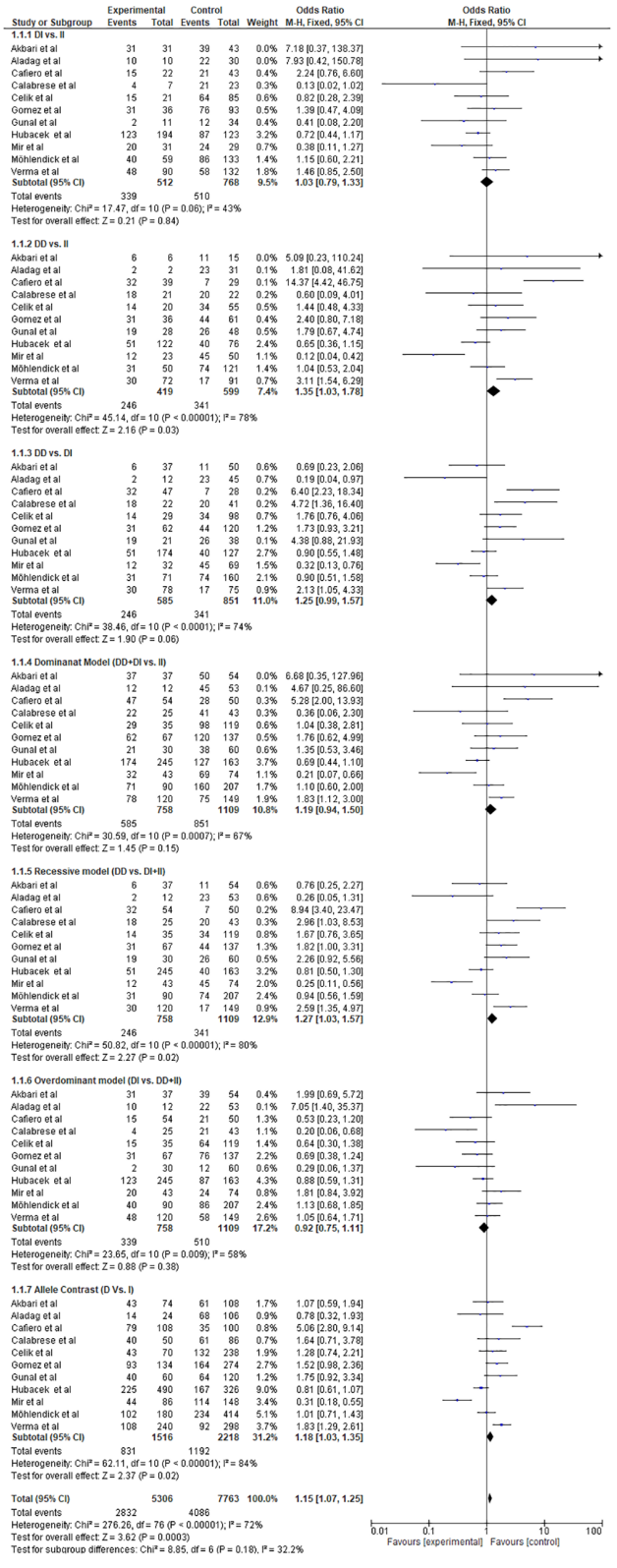

FIGURE 2 Forest plot showing the association of *ACE1* I/D rs1799752 polymorphism with the infection and severity of COVID-19.

were resolved through discussion if needed. We did not put any specific language restrictions during database searches.

2.2 | Eligibility criteria

Studies that analyzed the association of *ACE1* (NG_011648.1)I/D rs1799752 and/or *ACE2* (NG_012575.2) rs2285666 with the infection and/severity of COVID-19, designed as case–control analysis, contained sufficient data of genotypes or alleles frequency for odds ratios (ORs) and 95% confidence intervals (CIs) calculation and involved human subjects were included. In contrast, studies that did not analyze *ACE1* I/D rs1799752 and/or *ACE2* rs2285666 polymorphisms, contained no control arm, insufficient genotypes or alleles frequency, and did not involve human subjects were excluded.

2.3 | Data extraction

Both reviewers independently extracted the following information from literature using a precoded data form: name of the first author, year of study, country of publication, ethnicity, number of severe and non-severe cases, and genotypic information. For calculating the Hardy–Weinberg Equilibrium (HWE) *p*-value, we used the application in https://ihg.gsf.de/cgi-bin/hw/hwa1.pl.

2.4 | Data analysis

Association of *ACE1* I/D rs1799752 and/or *ACE2* rs2285666 polymorphisms with SARS-CoV-2 infection and severity was considered as the major outcome of this meta-analysis. Therefore, the ORs with 95% CIs were calculated for each study included using seven genetic association models, including allele (D vs. I), codominant 1 (DI vs. II), codominant 2 (DD vs. II), codominant 3 (DD vs. DI), dominant (DD + DI vs. II), recessive (DD vs. DI + II), and overdominant (DI vs. DD + II) models for *ACE1* I/D rs1799752, and allele (G vs. A), codominant 1 (GA vs. AA), codominant 2 (GG vs. AA), codominant 3 (GG vs. GA), dominant (GG + GA vs. AA), recessive (GG vs. GA + AA), and overdominant (GA vs. GG + AA) models for *ACE2* rs2285666, individually. For *ACE1* I/D rs1799752 polymorphism, the subjects were classified into two subgroups based on their ethnicity as Caucasian and Asian. The pooled results were evaluated using the random-effects model (the DerSimonian and Laird method) and the fixed-effects model (the Mantel–Haenszel method). A *p*-value of $< .05$ was considered statistically significant in terms of the association. In addition to this, I^2 (%) was calculated to test the heterogeneity. The probability of publication bias was assessed using a funnel plot (Duval & Tweedie, 2000)

and asymmetry was analyzed through Egger's regression (Egger et al., 1997) and Begg-Mazumdars (Begg & Mazumdar, 1994) tests. Moreover, we implemented sensitivity analysis to evaluate the influence of individual studies by deleting one study in each turn. All analyses in this study were completed using Review Manager (RevMan) version 5.4.1 (The Cochrane Collaboration, Oxford, UK).

3 | RESULTS

Our systemic search resulted in a total of 821 records from the aforementioned electronic databases. After removal of duplicates, and screening based on the eligible criteria, 16 full-text articles were assessed for eligibility. Due to the lack of insufficient genotype information, another 5 articles were removed, and finally, 11 studies were included in this meta-analysis (Akbari et al., 2021; Aladag et al., 2021; Cafiero et al., 2021; Calabrese et al., 2021; Çelik et al., 2021; Gómez et al., 2020; Gunal et al., 2021; Hubacek et al., 2021; Mir et al., 2021; Möhlendick et al., 2021; Verma et al., 2021). Among these, all studies evaluated the association of *ACE1* I/D rs1799752 polymorphism (severe cases = 758 and non-severe cases = 1109), while only 3 studies (Çelik et al., 2021; Gómez et al., 2020; Möhlendick et al., 2021) evaluated the association of *ACE2* rs2285666 polymorphism (severe cases = 192, non-severe cases = 464). Three studies were performed on the Asian population (Akbari et al., 2021; Mir et al., 2021; Verma et al., 2021) and 8 studies were performed on the Caucasian population (Aladag et al., 2021; Cafiero et al., 2021; Calabrese et al., 2021; Çelik et al., 2021; Gómez et al., 2020; Gunal et al., 2021; Hubacek et al., 2021; Möhlendick et al., 2021) for *ACE1* I/D rs1799752 polymorphism (Figure 1 and Table 1).

3.1 | Association of ACE1 I/D rs1799752 with the infection and severity of COVID-19

Pooled analysis showed that *ACE1* I/D rs1799752 polymorphism was correlated with the infection and severity of SARS-CoV-2 in recessive and allele models for the fixed-effects model (DD vs. DI + II: OR: 1.27, 95% CI: 1.02–1.59, *p*-value: .031, I^2: 80.32% and D vs. I: OR: 1.17, 95% CI: 1.02–1.35, *p*-value: .025, I^2: 83.90%) (Table 2 and Figure 2). Subgroup analysis showed that codominant 3, recessive, and allele model were associated with COVID-19 infection and severity for fixed-effects model (DD vs. DI: OR: 1.35, 95% CI: 1.03–1.78, *p*-value: .029, I^2: 72.44% and DD vs. DI + II: OR: 1.37, 95% CI: 1.07–1.76, *p*-value: .012, I^2: 76.38%, and D vs. I: OR: 1.20, 95% CI: 1.02–1.41, *p*-value: .031, I^2: 80.10%) in Caucasian ethnicity (Table 2).

3.2 | Association of ACE2 rs2285666 with the infection and severity of COVID-19

Pooled meta-regression analysis of *ACE2* rs2285666 with the infection and severity of COVID-19 (Table 3 and Figure 3) showed that codominant 3 (GG vs. GA: [OR: 2.63, 95% CI: 1.45–4.75, *p*-value: .001 for both random- and fixed-effects models], I^2: 0%), overdominant (GG vs. GA + AA: [OR: 1.97, 95% CI: 1.28–3.03, *p*-value: .002 for random-effects model and OR: 1.97, 95% CI: 1.29–3.00, *p*-value: .002 for fixed-effects model], I^2: 4.70%),

TABLE 3 Meta-analysis of the association of *ACE2* rs2285666 polymorphism with the infection and severity of COVID-19

Genetic models (*ACE2* rs2285666)	Test of heterogeneity		Test of association					
			Random-effects model			Fixed-effects model		
	p-value	I^2 (%)	OR	95% CI	*p*-value	OR	95% CI	*p*-value
GA vs. AA	.134	50.34	0.58	0.19–1.77	.341	0.59	0.27–1.30	.190
GG vs. AA	.163	44.94	1.48	0.69–3.17	.317	1.38	0.79–2.40	.257
GG vs. GA	.374	0	2.63	1.45–4.75	**.001**	2.63	1.45–4.75	**.001**
GG + GA vs. AA	.135	50.15	1.29	0.58–2.85	.531	1.19	0.69–2.06	.538
GG vs. GA + AA	.350	4.70	1.97	1.28–3.03	**.002**	1.97	1.29–3.00	**.002**
GA vs. GG + AA	.298	17.38	0.41	0.21–0.78	**.006**	0.41	0.23–0.74	**.003**
G vs. A	.069	62.64	1.66	0.96–2.86	.068	1.61	1.16–2.24	**.004**

Bold *p*-values indicate statistically significant.

and recessive model (GA vs. GG + AA: [OR: 0.41, 95% CI: 0.21–0.78, *p*-value: .006 for random-effects model and OR: 0.41, 95% CI: 0.23–0.74, *p*-value: .003 for fixed-effects model], I^2: 17.38%) were linked with severity of SARS-CoV-2 for both random-effects and fixed-effects models. Allele model of rs2285666 showed significant association for fixed-effects model only (G vs. A: OR: 1.61, 95% CI: 1.16–2.24, *p*-value: .004, I^2: 62.64%).

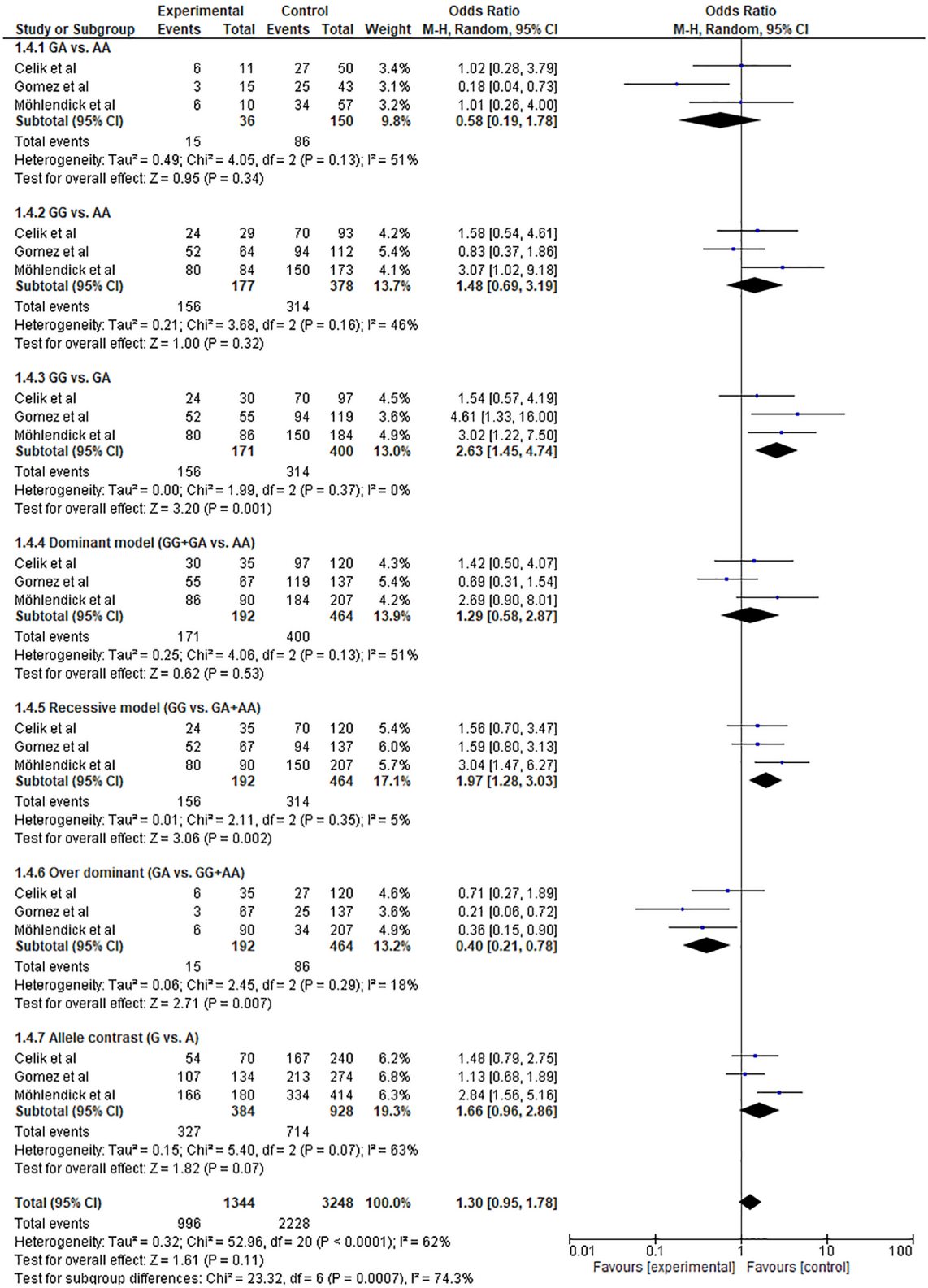

FIGURE 3 Forest plot showing the association of *ACE2* rs2285666 polymorphism with the infection and severity of COVID-19.

3.3 | Publication bias and sensitivity analysis

Table 4 and Figure 4 depict the publication bias analysis for both *ACE1* I/D rs1799752 and/or *ACE2* rs2285666 polymorphisms. No statistically significant publication bias was observed from Egger's test and Begg-Mazumdar's test (Table 4) or funnel plots (Figure 4). We also implemented sensitivity analysis in terms of the allele model for both SNPs (Figure 5), but no significant deviation was observed after excluding each study each time.

4 | DISCUSSION

Based on the recommendations for establishing more compact scientific evidence by Oscanoa et al. (2021), we performed the present meta-analysis to explore the association of *ACE1* and *ACE2* genetic polymorphisms with the severity of SARS-CoV-2 infected patients. Our current meta-analysis suggests that *ACE1* I/D rs1799752 and *ACE2* rs2285666 variants may increase the severity in SARS-CoV-2-infected patients. Recent investigations have revealed that genetic polymorphisms in both of these genes may have a significant role in COVID-19 severity (Calabrese et al., 2021; Cheng et al., 2020; Li, Wang et al., 2020).

The correlation of *ACE1* I/D rs1799752 polymorphism with the risk of various diseases has been studied previously. It was demonstrated that I/D variant can impose the risk of hypertension in African ethnicity (Mengesha et al., 2019), type 2 diabetes (T2DM) in Caucasian and East-Asian ethnicities (Zhou et al., 2010), and both hypertension and T2DM in Caucasian and Asian ethnicities (Liu et al., 2021), and chronic kidney disease in Asian hypertensive male patients (Lin et al., 2014) which are thought to get worsen during COVID-19 (Matta et al., 2020). During the COVID-19 pandemic, the role of this variant in the severity had also investigated by different studies. To establish comprehensive evidence, we have tried to retrieve all available studies and screened and analyzed these studies. Our analysis reported that *ACE1* I/D rs1799752 polymorphism might confer the severe condition in SARS-CoV-2 infected patients. Both DD genotype (OR: 1.27) and D allele (OR: 1.17) have demonstrated the correlation with the severity in the overall population (both Caucasian and Asian). The risk associated with the severity is also observed in the Caucasian population for DD genotype (OR: 1.35 in DD vs. DI and OR: 1.37 in DD vs. DI + II), and D allele (OR: 1.20). Studies on COVID-19 patients also revealed that I/D rs1799752 is associated with the severity (Akbari et al., 2021; Aladag et al., 2021; Cafiero et al., 2021; Calabrese et al., 2021; Gómez et al., 2020; Gunal et al., 2021; Hubacek et al., 2021; Mir et al., 2021; Verma et al., 2021), which is consistent with our overall findings. However, two studies reported no significant association between *ACE1* I/D polymorphism and COVID-19 severity (Çelik et al., 2021; Möhlendick et al., 2021).

Genetic polymorphisms in the *ACE2* gene may alter the expression level and binding affinity of SARS-CoV-2 in the host (Cao et al., 2020; Darbani, 2020; Gemmati et al., 2020; Hou et al., 2020). A common polymorphism in *ACE2* is rs2285666, the association of which had been analyzed for the severe outcome in SARS-CoV-2 infected patients (Cafiero et al., 2021; Çelik et al., 2021;Gómez et al., 2020; Möhlendick et al., 2021). Although it is evident that COVID-19 comorbidities like cerebral stroke, CHD, T2DM, and hypertension are correlated to rs2285666 polymorphism (Chen et al., 2021; Pinheiro et al., 2019; Wu et al., 2017; Yang et al., 2015), recent studies showed conflicting outcomes. Only three studies evaluated the role of this SNP in COVID-19 patients (Gómez et al., 2020; Möhlendick et al., 2021), among which two studies reported a statistically significant association with severe clinical outcomes, while another one did not suggest any significant correlation (Çelik et al., 2021). To provide more comprehensive evidence, we performed a meta-analysis with these three studies, which showed that codominant 3 (GG vs. GA: OR: 2.63), overdominant (GG vs. GA + AA:

TABLE 4 Publication bias analysis

	Publication Bias (*p*-value)	
Genetic model	**Egger's test**	**Begg-Mazumdar's test**
ACE1 I/D rs1799752		
DI vs. II	0.924	0.815
DD vs. II	0.655	0.815
DD vs. DI	0.582	0.686
DD + DI vs. II	0.684	0.697
DD vs. DI + II	0.711	0.586
DI vs. DD + II	0.899	0.815
D vs. I	0.601	0.697
ACE2 rs2285666		
GA vs. AA	0.449	0.117
GG vs. AA	0.256	0.117
GG vs. GA	0.686	0.602
GG + GA vs. AA	0.199	0.117
GG vs. GA + AA	0.957	0.602
GA vs. GG + AA	0.598	0.602
G vs. A	0.564	0.602

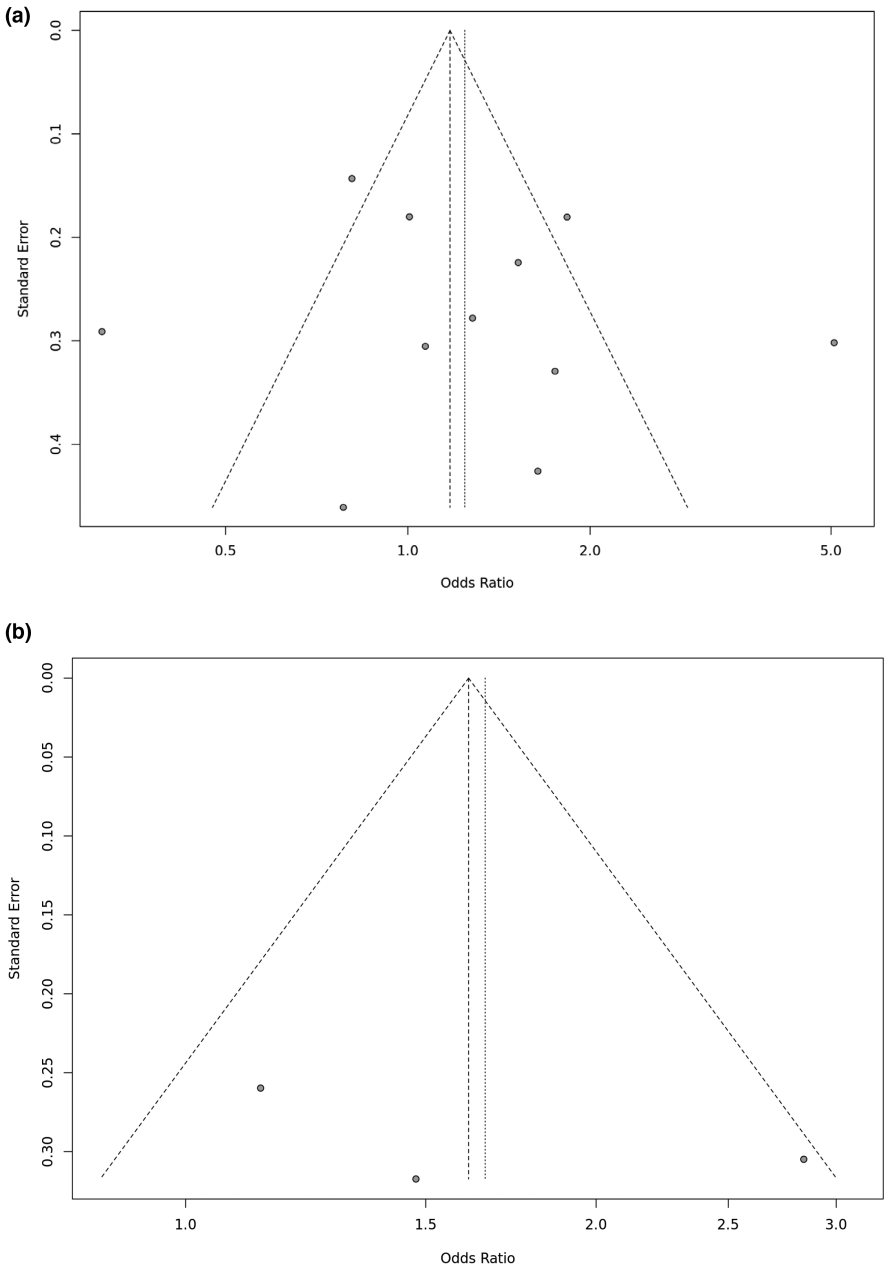

FIGURE 4 Funnel plots in allele model: (a) *ACE* I/D rs1799752 (b) *ACE2* rs2285666.

OR: 1.97 (random-effects model) and OR: 1.97 (fixed-effects model)), and recessive model (GA vs. GG + AA: OR: 0.41 (random-effects model), and OR: 0.41 (fixed-effects model)) are correlated with the severity of SARS-CoV-2. G allele of rs2285666 was also reported to be significantly linked with the severity for the fixed-effects model (G vs. A: OR: 1.61). Moreover, there was no notable publication bias in our analysis, and the implementation of sensitivity analysis confirmed the stability of our results.

Although Oscanoa et al. (2021) performed the first meta-analysis with *ACE1* I/D polymorphism, we have performed the first meta-analysis, including *ACE1* I/D rs1799752 and *ACE2* rs2285666 variants. Besides, we have included comparatively large number studies (11 studies) with *ACE1* I/D polymorphism (severe cases = 758 and non-severe cases = 1109), with *ACE2* rs2285666 polymorphism (severe cases = 192, non-severe cases = 464) that includes population from both Caucasian and Asian ancestry. Furthermore, publication bias and sensitivity analyses validated the stability of the findings. Despite this, our study still lacks some merits. To mention, there is still no study on African or other ethnicities except Asian and Caucasian, which may somehow limit the acceptability of the overall findings. Again, the number of studies is still short to conclude any compact association. We suggest conducting a further meta-analysis to establish the association of *ACE1* rs1799752 and *ACE2* rs2285666 polymorphisms with the severity of COVID-19.

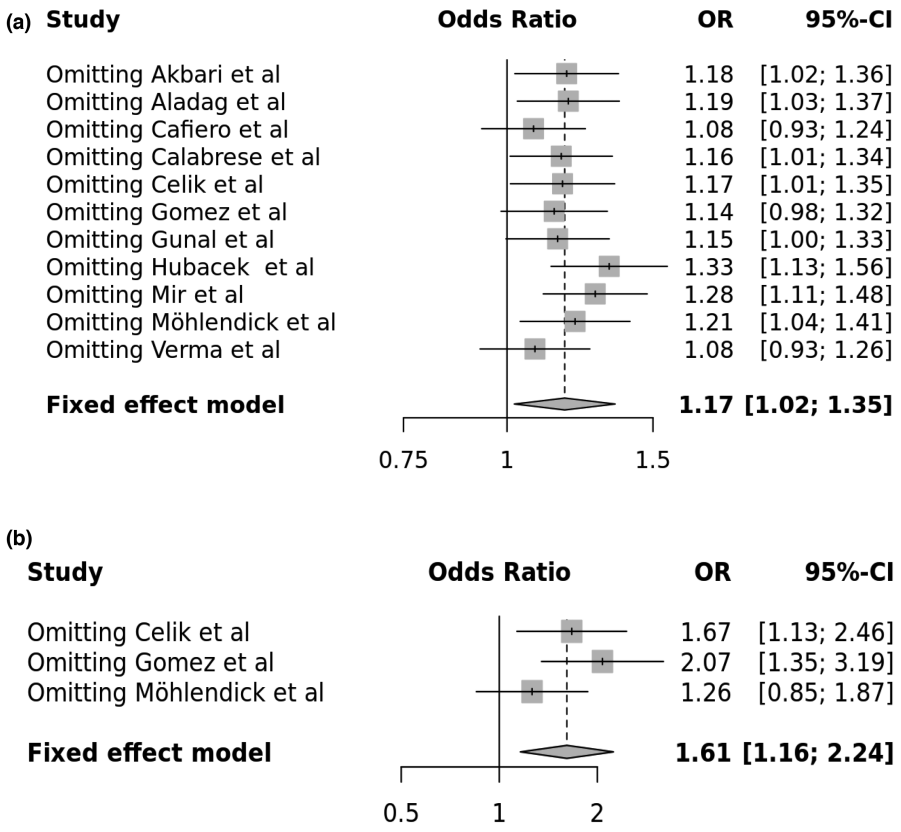

FIGURE 5 Sensitivity analysis in allele model: (a) *ACE* I/D rs1799752 (b) *ACE2* rs2285666.

5 | CONCLUSION

The present meta-analysis suggests that *ACE1* I/D rs1799752 and *ACE2* rs2285666 variants may enhance the severity in SARS-CoV-2 infected patients. However, future investigations, including studies from all ethnicities and other genetic polymorphisms, are warranted to verify the actual correlation between COVID-19 infection and subsequent severity.

AUTHOR CONTRIBUTIONS

Md. Abdul Aziz performed the literature search and data acquisition. **Mohammad Safiqul Islam** performed all the statistical analyses related to this meta-analysis. **Md. Abdul Aziz** prepared the draft of the manuscript. **Mohammad Safiqul Islam** supervised and made substantial contributions to conception, design, data analysis, and data interpretation and revised the manuscript critically for important intellectual content.

ACKNOWLEDGMENTS

We are thankful to the Laboratory of Pharmacogenomics and Molecular Biology, Department of Pharmacy, Noakhali Science and Technology University, Sonapur-3814, Noakhali, Bangladesh, for their support.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ETHICS STATEMENT

None required.

ORCID

Md. Abdul Aziz https://orcid.org/0000-0003-2079-4509
Mohammad Safiqul Islam https://orcid.org/0000-0003-4924-5319

REFERENCES

Akbari, M., Taheri, M., Mehrpoor, G., Eslami, S., Hussen, B. M., Ghafouri-Fard, S., & Arefian, N. (2021). Assessment of ACE1 variants and ACE1/ACE2 expression in COVID-19 patients. *Vascular Pharmacology*, *142*, 106934. Advance online publication. https://doi.org/10.1016/j.vph.2021.106934

Aladag, E., Tas, Z., Ozdemir, B. S., Akbaba, T. H., Akpınar, M. G., Goker, H., Unalan-Altintop, T., Inkaya, A. C., Alp, A., Metan, G., Haznedaroglu, I. C., Balci-Peynircioglu, B., & Sayinalp, N. (2021). Human ace D/I polymorphism could affect the clinicobiological course of COVID-19. *Journal of the Renin-Angiotensin-Aldosterone System: JRAAS*, *2021*, 5509280. https://doi.org/10.1155/2021/5509280

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, *50*(4), 1088–1101.

Cafiero, C., Rosapepe, F., Palmirotta, R., Re, A., Ottaiano, M. P., Benincasa, G., Perone, R., Varriale, E., D'Amato, G., Cacciamani, A., Micera, A., & Pisconti, S. (2021). Angiotensin system polymorphisms' in SARS-CoV-2 positive patients: Assessment between symptomatic and asymptomatic patients: A pilot study. *Pharmacogenomics and personalized medicine*, *14*, 621–629. https://doi.org/10.2147/PGPM.S303666

Calabrese, C., Annunziata, A., Coppola, A., Pafundi, P. C., Guarino, S., Di Spirito, V., Maddaloni, V., Pepe, N., & Fiorentino, G. (2021). ACE gene I/D polymorphism and acute pulmonary embolism in COVID19 pneumonia: A potential predisposing role. *Frontiers in Medicine*, *7*, 631148. https://doi.org/10.3389/fmed.2020.631148

Cao, Y., Li, L., Feng, Z., Wan, S., Huang, P., Sun, X., Wen, F., Huang, X., Ning, G., & Wang, W. (2020). Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell discovery*, *6*, 11. https://doi.org/10.1038/s41421-020-0147-1

Çelik, S. K., Genç, G. C., Pişkin, N., Açikgöz, B., Altinsoy, B., İşsiz, B. K., & Dursun, A. (2021). Polymorphisms of ACE (I/D) and ACE2 receptor gene (Rs2106809, Rs2285666) are not related to the clinical course of COVID-19: A case study. *Journal of Medical Virology*, *93*(10), 5947–5952. https://doi.org/10.1002/jmv.27160

Chen, F., Zhang, Y., Li, X., Li, W., Liu, X., & Xue, X. (2021). The impact of ACE2 polymorphisms on COVID-19 disease: Susceptibility, severity, and therapy. *Frontiers in Cellular and Infection Microbiology*, *11*, 753721. https://doi.org/10.3389/fcimb.2021.753721

Cheng, H., Wang, Y., & Wang, G. Q. (2020). Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *Journal of Medical Virology*, *92*(7), 726–730. https://doi.org/10.1002/jmv.25785

Darbani, B. (2020). The expression and polymorphism of entry machinery for COVID-19 in human: Juxtaposing population groups, gender, and different tissues. *International Journal of Environmental Research and Public Health*, *17*(10), 3433. https://doi.org/10.3390/ijerph17103433

Delanghe, J. R., Speeckaert, M. M., & De Buyzere, M. L. (2020). COVID-19 infections are also affected by human ACE1 D/I polymorphism. *Clinical Chemistry and Laboratory Medicine*, *58*(7), 1125–1126. https://doi.org/10.1515/cclm-2020-0425

Devaux, C. A., Rolain, J. M., & Raoult, D. (2020). ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. *Journal of Microbiology, Immunology, and Infection*, *53*(3), 425–435. https://doi.org/10.1016/j.jmii.2020.04.015

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*(2), 455–463. https://doi.org/10.1111/j.0006-341x.2000.00455.x

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed.)*, *315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Gemmati, D., Bramanti, B., Serino, M. L., Secchiero, P., Zauli, G., & Tisato, V. (2020). COVID-19 and individual genetic susceptibility/receptivity: Role of ACE1/ACE2 Genes, immunity, inflammation and coagulation. might the double X-chromosome in females be protective against SARS-CoV-2 compared to the single X-chromosome in males? *International Journal of Molecular Sciences*, *21*(10), 3474. https://doi.org/10.3390/ijms21103474

Gómez, J., Albaiceta, G. M., García-Clemente, M., López-Larrea, C., Amado-Rodríguez, L., Lopez-Alonso, I., Hermida, T., Enriquez, A. I., Herrero, P., Melón, S., Alvarez-Argüelles, M. E., Boga, J. A., Rojo-Alba, S., Cuesta-Llavona, E., Alvarez, V., Lorca, R., & Coto, E. (2020). Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. *Gene*, *762*, 145102. https://doi.org/10.1016/j.gene.2020.145102

Gunal, O., Sezer, O., Ustun, G. U., Ozturk, C. E., Sen, A., Yigit, S., & Demirag, M. D. (2021). Angiotensin-converting enzyme-1 gene insertion/deletion polymorphism may be associated with COVID-19 clinical severity: A prospective cohort study. *Annals of Saudi Medicine*, *41*(3), 141–146. https://doi.org/10.5144/0256-4947.2021.141

Hatami, N., Ahi, S., Sadeghinikoo, A., Foroughian, M., Javdani, F., Kalani, N., Fereydoni, M., Keshavarz, P., & Hosseini, A. (2020). Worldwide ACE (I/D) polymorphism may affect COVID-19 recovery rate: An ecological meta-regression. *Endocrine*, *68*(3), 479–484. https://doi.org/10.1007/s12020-020-02381-7

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*(2), 271–280.e8. https://doi.org/10.1016/j.cell.2020.02.052

Hou, Y., Zhao, J., Martin, W., Kallianpur, A., Chung, M. K., Jehi, L., Sharifi, N., Erzurum, S., Eng, C., & Cheng, F. (2020). New insights into genetic susceptibility of COVID-19: An ACE2 and TMPRSS2 polymorphism analysis. *BMC Medicine*, *18*(1), 216. https://doi.org/10.1186/s12916-020-01673-z

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Hubacek, J. A., Dusek, L., Majek, O., Adamek, V., Cervinkova, T., Dlouha, D., & Adamkova, V. (2021). ACE I/D polymorphism in Czech first-wave SARS-CoV-2-positive survivors. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *519*, 206–209. https://doi.org/10.1016/j.cca.2021.04.024

Li, Y., Zhou, W., Yang, L., & You, R. (2020). Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. *Pharmacological Research*, *157*, 104833. https://doi.org/10.1016/j.phrs.2020.104833

Li, Z., Wang, S., Jiao, X., & Wei, G. (2020). Genetic association of angiotensin-converting enzyme I/D polymorphism with intracranial hemorrhage: An updated meta-analysis of 39 case-control studies. *World Neurosurgery*, *134*, e1–e7. https://doi.org/10.1016/j.wneu.2019.06.104

Lin, C., Yang, H. Y., Wu, C. C., Lee, H. S., Lin, Y. F., Lu, K. C., Chu, C. M., Lin, F. H., Kao, S. Y., & Su, S. L. (2014). Angiotensin-converting enzyme insertion/deletion polymorphism contributes high risk for chronic kidney disease in Asian male with hypertension—A meta-regression analysis of 98 observational studies. *PLoS One*, *9*(1), e87604. https://doi.org/10.1371/journal.pone.0087604

Lin, P., Li, H., Yu, T., & Liu, Y. (2019). The effect of angiotensin-converting enzyme gene polymorphisms on the clinical efficacy of perindopril prescribed for acute myocardial infarction in chinese han patients. *Genetic Testing and Molecular Biomarkers*, *23*(5), 316–324. https://doi.org/10.1089/gtmb.2018.0232

Liu, M., Yi, J., & Tang, W. (2021). Association between angiotensin converting enzyme gene polymorphism and essential hypertension: A systematic review and meta-analysis. *Journal of the Renin-Angiotensin-Aldosterone System: JRAAS*, *22*(1), 1–12. https://doi.org/10.1177/1470320321995074

Livshits, L. A., Harashchenko, T. A., Umanets, T. R., Krasnienkov, D. S., Gorodna, O. V., Podolskiy, V. V., Kaminska, T. M., Lapshyn, V. F., Podolskiy, V. V., & Antipkin, Y. G. (2021). Relationship between the prevalence of ACE1 I/D polymorphism genotype II and Covid-19 morbidity, mortality in Ukraine and in some Europe countries. *Cytology and Genetics*, *55*(5), 427–432. https://doi.org/10.3103/S0095452721050054

Matta, S., Chopra, K. K., & Arora, V. K. (2020). Morbidity and mortality trends of Covid 19 in top 10 countries. *The Indian Journal of Tuberculosis*, *67*(4S), S167–S172. https://doi.org/10.1016/j.ijtb.2020.09.031

Mengesha, H. G., Petrucka, P., Spence, C., & Tafesse, T. B. (2019). Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: A meta-analysis and systematic review. *PLoS One*, *14*(2), e0211054. https://doi.org/10.1371/journal.pone.0211054

Mir, M. M., Mir, R., Alghamdi, M., Alsayed, B. A., Wani, J. I., Alharthi, M. H., & Al-Shahrani, A. M. (2021). Strong association of angiotensin converting enzyme-2 gene insertion/deletion polymorphism with susceptibility to SARS-CoV-2, hypertension, coronary artery disease and COVID-19 disease mortality. *Journal of personalized medicine*, *11*(11), 1098. https://doi.org/10.3390/jpm11111098

Möhlendick, B., Schönfelder, K., Breuckmann, K., Elsner, C., Babel, N., Balfanz, P., Dahl, E., Dreher, M., Fistera, D., Herbstreit, F., Hölzer, B., Koch, M., Kohnle, M., Marx, N., Risse, J., Schmidt, K., Skrzypczyk, S., Sutharsan, S., Taube, C., … Kribben, A. (2021). ACE2 polymorphism and susceptibility for SARS-CoV-2 infection and severity of COVID-19. *Pharmacogenetics and Genomics*, *31*(8), 165–171. https://doi.org/10.1097/FPC.0000000000000436

Novelli, A., Biancolella, M., Borgiani, P., Cocciadiferro, D., Colona, V. L., D'Apice, M. R., Rogliani, P., Zaffina, S., Leonardis, F., Campana, A., Raponi, M., Andreoni, M., Grelli, S., & Novelli, G. (2020). Analysis of ACE2 genetic variants in 131 Italian SARS-CoV-2-positive patients. *Human Genomics*, *14*(1), 29. https://doi.org/10.1186/s40246-020-00279-z

Oscanoa, T. J., Vidal, X., Coto, E., & Romero-Ortuno, R. (2021). ACE gene I/D polymorphism and severity of SARS-CoV-2 infection in hospitalized patients: A meta-analysis. *Arterial Hypertension*, *25*(3), 112–118. https://doi.org/10.5603/AH.a2021.0018

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed.)*, *372*, n71. https://doi.org/10.1136/bmj.n71

Parit, R., & Jayavel, S. (2021). Association of ACE inhibitors and angiotensin type II blockers with ACE2 overexpression in COVID-19 comorbidities: A pathway-based analytical study. *European Journal of Pharmacology*, *896*, 173899. https://doi.org/10.1016/j.ejphar.2021.173899

Pati, A., Mahto, H., Padhi, S., & Panda, A. K. (2020). ACE deletion allele is associated with susceptibility to SARS-CoV-2 infection and mortality rate: An epidemiological study in the Asian population. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *510*, 455–458. https://doi.org/10.1016/j.cca.2020.08.008

Peng, R., Wu, L. A., Wang, Q., Qi, J., & Gao, G. F. (2021). Cell entry by SARS-CoV-2. *Trends in Biochemical Sciences*, *46*(10), 848–860. https://doi.org/10.1016/j.tibs.2021.06.001

Pinheiro, D. S., Santos, R. S., Jardim, P., Silva, E. G., Reis, A., Pedrino, G. R., & Ulhoa, C. J. (2019). The combination of ACE I/D and ACE2 G8790A polymorphisms revels susceptibility to hypertension: A genetic association study in Brazilian patients. *PLoS One*, *14*(8), e0221248. https://doi.org/10.1371/journal.pone.0221248

Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., & Soubrier, F. (1990). An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *The Journal of Clinical Investigation*, *86*(4), 1343–1346. https://doi.org/10.1172/JCI114844

Saadat, M. (2020). No significant correlation between ACE Ins/Del genetic polymorphism and COVID-19 infection. *Clinical Chemistry and Laboratory Medicine*, *58*(7), 1127–1128. https://doi.org/10.1515/cclm-2020-0577

Verma, S., Abbas, M., Verma, S., Khan, F. H., Raza, S. T., Siddiqi, Z., Ahmad, I., & Mahdi, F. (2021). Impact of I/D polymorphism of angiotensin-converting enzyme 1 (ACE1) gene on the severity of COVID-19 patients. *Infection, Genetics and Evolution*, *91*, 104801. https://doi.org/10.1016/j.meegid.2021.104801

Wu, Y. H., Li, J. Y., Wang, C., Zhang, L. M., & Qiao, H. (2017). The ACE2 G8790A polymorphism: Involvement in type 2 diabetes mellitus combined with cerebral stroke. *Journal of Clinical Laboratory Analysis*, *31*(2), e22033. https://doi.org/10.1002/jcla.22033

Yamamoto, N., Ariumi, Y., Nishida, N., Yamamoto, R., Bauer, G., Gojobori, T., Shimotohno, K., & Mizokami, M. (2020). SARS-CoV-2 infections and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. *Gene*, *758*, 144944. https://doi.org/10.1016/j.gene.2020.144944

Yamamoto, N., Nishida, N., Yamamoto, R., Gojobori, T., Shimotohno, K., Mizokami, M., & Ariumi, Y. (2021). *Angiotensin-Converting Enzyme (ACE) 1* gene polymorphism and phenotypic expression of COVID-19 symptoms. *Genes*, *12*(10), 1572. https://doi.org/10.3390/genes12101572

Yang, M., Zhao, J., Xing, L., & Shi, L. (2015). The association between angiotensin-converting enzyme 2 polymorphisms and essential hypertension risk: A meta-analysis involving 14,122 patients. *Journal of the Renin-Angiotensin-Aldosterone System: JRAAS*, *16*(4), 1240–1244. https://doi.org/10.1177/1470320314549221

Yoo, K. H., Yim, H. E., Bae, E. S., & Hong, Y. S. (2017). Genetic contributions to childhood obesity: Association of candidate gene polymorphisms and overweight/obesity in Korean preschool

children. *Journal of Korean Medical Science*, *32*(12), 1997–2004. https://doi.org/10.3346/jkms.2017.32.12.1997

Yuan, Y., Meng, L., Zhou, Y., & Lu, N. (2017). Genetic polymorphism of angiotensin-converting enzyme and hypertrophic cardiomyopathy risk: A systematic review and meta-analysis. *Medicine*, *96*(48), e8639. https://doi.org/10.1097/MD.0000000000008639

Zhou, J. B., Yang, J. K., Lu, J. K., & An, Y. H. (2010). Angiotensin-converting enzyme gene polymorphism is associated with type 2 diabetes: A meta-analysis. *Molecular Biology Reports*, *37*(1), 67–73. https://doi.org/10.1007/s11033-009-9648-6

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., Tan, W., & China Novel Coronavirus Investigating and Research Team. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England Journal of Medicine*, *382*(8), 727–733. https://doi.org/10.1056/NEJMoa2001017

How to cite this article: Aziz, M. A., & Islam, M. S. (2022). Association of *ACE1* I/D rs1799752 and *ACE2* rs2285666 polymorphisms with the infection and severity of COVID-19: A meta-analysis. *Molecular Genetics & Genomic Medicine*, *10*, e2063. https://doi.org/10.1002/mgg3.2063