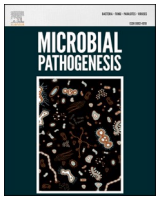
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Microbial Pathogenesis 172 (2022) 105781

Contents lists available at ScienceDirect

Microbial Pathogenesis

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



Global distribution of ACE1 (rs4646994) and ACE2 (rs2285666) polymorphisms associated with COVID-19: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
ACE2 receptor
COVID-19
SARS-CoV-2
rs4646994
rs2285666

ABSTRACT

Background: Recent studies emphasize the significant impact of the renin-angiotensin aldosterone system (RAAS) as a risk factor associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, according to the literature, the effect of rs4646994 and rs2285666 polymorphisms on susceptibility and progression to severe clinical outcomes is still controversial. Our aim was to investigate the effect of polymorphisms such as rs4646994 and rs2285666 on susceptibility to coronavirus disease-2019 (COVID-19).

Methods: We conducted a comprehensive literature search using databases such as ISI Web of Science, PubMed, Scopus, and Google Scholar to retrieve studies on the effect of two polymorphisms (rs4646994 and rs2285666) of the angiotensin-converting enzyme (ACE) gene on COVID-19. Finally, the effect of each polymorphism on SARS-CoV-2 infection was measured based on the odds ratio with 95% confidence intervals.

Results: Analysis of the rs4646994 polymorphism showed that the frequency of the D allele in patients infected with COVID-19 was higher than that the I allele. Moreover, the authors found that the DD genotype increased the risk of severe disease by 1.7-fold in Asian population, whereas, this was not the case in the Western population. However, the rs4646994 II genotype plays a protective role against COVID-19 in Western countries. In the case of the rs2285666 polymorphism based on patient ethnicity, the C allele had the highest frequency. Interestingly, in people harboring the GG and TT genotypes, the risk of progression to severe disease significantly increased, while people with genotypes such as GA, AA and CC seem to be more resistant to severe Covid-19.

Conclusions: Based on geographical region, the rs4646994 DD genotype may be considered as a predictive biomarker to identify the susceptibility of human to SARS-CoV-2 infection and severe COVID-19 outcomes. We also concluded that individuals with GG and TT genotypes are significantly more susceptible to severe outcomes of disease, while conversely, individuals with GA, AA, and CC genotypes are less susceptible to severe COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the causes of atypical pneumonia, which first appeared in December 2019, and due to its global spread, the World Health Organization (WHO) declared a global pandemic of this virus on 11 March 2020 [1]. Nearly two years after the outbreak of this virus, according to the WHO report, so far more than 453 million cases have been infected with SARS-CoV-2, and 6.03 million people have died (https://covid19.who.int/). People infected with coronavirus disease-2019 (COVID-19) show a variety of symptoms, although most people experience mild symptoms or remain asymptomatic carriers, some of them develop into the acute respiratory distress syndrome (ARDS) [2,3]. According to the literature, comorbidities such as male sex, age over 60 years, African-American race, obesity, hypertension, and diabetes are the most common cofactors associated with severe outcomes as well as high mortality [4].

Evidence suggests that the renin-angiotensin aldosterone system (RAAS) is an enzymatic cascade that plays an important role in the pathogenesis of COVID-19 [5]. In this pathway, the angiotensin-converting enzyme (ACE or ACE1) converts angiotensin-1 (Ang-1) to Ang-2; on the other hand, ACE2 converts Ang-2 to Ang-(1-7) [6]. Through binding to AT1 receptor, Ang-2 induces thrombosis, inflammation, fibrosis, and vasoconstriction, while

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https://doi.org/10.1016/j.micpath.2022.105781
Received 15 April 2022; Received in revised form 7 September 2022; Accepted 10 September 2022
Available online 15 September 2022

Table 1
Characteristics of the included studies.

First author	Year	Country	rs4646994										
			Allele, n				Genotypes, n						
			I		D		DD		DI		II		*p*-HWE
			Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients
Gomez	2020	Spain	NA	NA	NA	NA	75	195	107	256	22	85	NA
Kouhpayeh	2021	Iran	139	225	377	263	144	70	89	123	25	51	0.052
Celik	2021	Turkey	120	NA	110	NA	48	NA	79	NA	27	NA	NA
Mir	2021	Saudi Arabia	NA	NA	NA	NA	57	60	44	50	16	40	NA
Hubacek	2021	Czech Republic	317	1878	301	2032	91	701	210	1331	107	547	NA
Mohlendick	2021	Germany	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Verma	2021	India	338	NA	200	NA	47	NA	106	NA	116	NA	NA
Gunal	2021	Turkey	NA	NA	NA	NA	45	NA	14	NA	31	NA	NA
Calabrese	2021	Italy	30	NA	63	NA	38	NA	25	NA	5	NA	NA
Aladag	2021	Turkey	75	351	149	249	45	77	59	95	8	128	NA
Annunziata	2021	Italy	NA	NA	NA	NA	17	8	2	8	1	3	NA
Papadopoulou	2021	Greece	NA	NA	NA	NA	39	115	21	150	13	51	NA
Gomez	2022	Mexico	587	NA	375	NA	77	NA	221	NA	183	NA	0.37
Molina	2022	Spain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Abdelsattar	2022	Egypt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Alimoradi	2022	Iran	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jevnikar	2022	Slovenia	NA	NA	NA	NA	24	27	32	49	11	20	0.95
Mahmood	2022	Iraq	74	63	124	129	39	41	46	47	14	8	0.941
Gong	2022	China	NA	NA	NA	NA	128	57	177	228	116	156	NA

Ang-(1-7) binds to AT2 receptor and hinders the reactions involved in fibrosis, thrombosis, and inflammation [7,8]. Interaction between ACE1/ACE2 predicts the risk of disorders such as hypertension, cardiovascular disease (CVD), and pulmonary diseases, hence, the ACE1/ACE2 axis influences the risk factors involved in COVID-19, and also plays a key role in susceptibility to severe clinical outcomes [9–11]. In addition, SARS-CoV-2 uses its spike protein to bind to the ACE2 receptor and entry into host cells [12]. Recent experiments showed that monoclonal antibodies significantly block SARS-CoV-2 entry into human cells [13].

According to the recent literature, both acquired and inherited factors alter the expression and biological function of RAAS modules and ultimately affect the outcomes of SARS-CoV-2 infection; for example, reduction in ACE2 expression might have a role in hypertension, diabetes mellitus, as well as lung injury in infections caused by influenza virus and SARS-CoV-2 in animal models [14–16]. Furthermore, ACE2 expression reduces with age, especially in men [17]. This may explain why deaths from COVID-19 are lower in older men than in children.

The ACE gene locates on the long arms of chromosome, and contains 26 exons; various studies have investigated the role of insertion/deletion (I/D) of a 287-bp alu repeat sequence in intron 16 (rs4646994) and its relationship with complications caused by SARS-CoV-2 such as heart failure, hypertension, diabetes, kidney failure, and pneumonia [17–21]. Allelic variations of the ACE2 gene are divided into three distinct genotypes including II, ID, and DD; in this regard, individuals carrying the DD genotype have highest ACE blood levels, which in turn increases the risk of stroke and diabetic nephropathy [22,23]. Moreover, high frequency of the DD genotype in Western countries is associated with high mortality of COVID-19 compared to the Asian populations [24].

The ACE2 gene have 22 exons and locates on the X chromosome (Xp22.2); this gene contains several single nucleotide polymorphisms (SNPs), and G to A change at nucleotide +4 of intron 3 (SNP rs2285666) increases the risk of heart failure and hypertension due to increase the expression of ACE2 receptor [25,26]. Due to the presence of only one X chromosome in men, ACE2 expression is lower in them than in women, which in turn leads to an increase in the severity of COVID-19 in men [27,28]. However, the effect of genetic diversity on RAAS components and susceptibility to SARS-CoV-2 is still unclear. In this study we evaluated the global distribution of the rs4646994 and rs2285666 polymorphisms associated with COVID-19; we also assessed the impact of these polymorphisms on susceptibility to and severity of COVID-19 in patients.

2. Methods

2.1. Search strategy

First, until July 2022, we conducted a systematic literature search using global databases such as ISI Web of Science, PubMed, Scopus, and Google Scholar. All studies on the rs2285666 and rs4646994 polymorphisms associated with SARS-CoV-2 infection were retrieved regardless of language limitation. We used several keywords such as "ACE", "ACE2", "Renin-angiotensin aldosterone system", "Single nucleotide polymorphism", "genetic variation", "rs2285666", "rs4646994", "SARS-CoV-2", "COVID-19", and "acute respiratory distress". In addition, bibliographies of articles were manually reviewed by two separate authors to avoid missing additional relevant studies.

2.2. Inclusion criteria

The inclusion criteria were: 1) articles as original, cohort, retrospective, perspective, cross-sectional; 2) articles on the effect of the rs2285666 and rs4646994 polymorphisms in susceptibility to COVID-19; 3) articles on the effect of the rs2285666 and rs4646994 polymorphisms in developing primary infection to severe COVID-19 infection; 4) studies on human population; 5) articles with available full-text.

2.3. Exclusion criteria

The exclusion criteria were: 1) letters, case reports, and review articles; 2) studies on other polymorphisms (except rs2285666 and rs4646994) in COVID-19 patients; 3) in vivo or in vitro studies; 4) studies with unclear methods/results.

2.4. Data collection

In the present study, we used the Newcastle-Ottawa Quality Assessment Scale (NOS) to evaluate the quality of studies. According to

rs4646994	rs2285666												Ref
Genotypes, n	Allele, n				Genotypes, n								
p-HWE	G/C		A/T		GG/CC		GA/CT		AA/TT		*p*-HWE		
Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	
NA	58/NA	124/NA	146/NA	374/NA	NA	NA	NA	NA	NA	NA	NA	NA	[29]
0.90	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[30]
NA	NA/57	NA	NA/21	NA	NA/37	NA	NA/33	NA	NA/7	NA	0.942	NA	[31]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[32]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[33]
NA	NA	NA	NA	NA	230/NA	178/NA	40/NA	35/NA	27/NA	40/NA	0.53	0.65	[34]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[35]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[36]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[37]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[38]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[39]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[40]
NA	NA/567	NA	NA/395	NA	NA/241	NA	NA/85	NA	NA/155	NA	0.001	NA	[41]
NA	NA	NA	NA	NA	58/NA	NA	22/NA	NA	8/NA	NA	0.076	NA	[42]
NA	NA/414	NA/249	NA/184	NA/45	NA/196	NA/114	NA/22	NA/21	NA/81	NA/12	NA	NA	[43]
NA	58/NA	34/NA	6/NA	17/NA	66/NA	24/NA	11/NA	19/NA	2/NA	7/NA	NA	NA	[44]
0.78	NA	NA	NA	NA	49/NA	65/NA	5/NA	22/NA	14/NA	9/NA	0.26	0.31	[45]
0.279	69/NA	80/NA	29/NA	16/NA	26/NA	33/NA	17/NA	14/NA	6/NA	1/NA	0.241	0.729	[46]
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[47]

the defined criteria, titles, abstracts, and full-text of articles were reviewed by two separate authors. In this meta-analysis, characteristics such as first author, publication year, country, allelic/genotype distribution of rs4646994, and allelic/genotype distribution of rs2285666 were considered as eligible criteria (Table 1) [29–47].

2.5. Statistical analysis

We pooled the data of eligible studies using Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ). The frequency of alleles and genotypes of these two variants (rs4646994 and rs2285666) was measured with event rate corresponding 95% confidence intervals (95% CIs). In addition, using odds ratio (OR), we computed the association between theses polymorphisms and susceptibility to the severe clinical outcomes of SARS-CoV-2 infection. Inter-study heterogeneity was appraised using indexes as I-squared and Cochran Q test. We also pooled the data in significant heterogeneity cases using the DerSimonial and Laird random effects model. Furthermore, publication bias was measured based on Begg's *p* value, Egger's *p* value, and asymmetry of funnel plot [48].

3. Results

3.1. Characteristics of included studies

Overall, 506 articles were retrieved during the literature search process. After evaluating titles, abstracts, and full-text with our inclusion criteria, 19 eligible articles were selected for statistical analysis (Fig. 1). The main reasons for omitting unrelated studies were: 1) investigating the non-rs2285666 and non-rs4646994 polymorphisms; 2) differences in purposes of studies; 3) lack of sufficient data; 4) article type. After careful review of 19 studies, information on the rs2285666 and rs4646994 polymorphisms in patients with COVID-19 and control individuals was retrieved and listed in Table 1.

3.2. Quality assessment

During the quality evaluation, two authors evaluated the quality of the studies based on three items: selection, comparison and exposure. Of these, 12 had high quality (7-9 stars), whereas, 7 studies had moderate quality. The studies had been conducted in countries such as Iraq, Iran, Mexico, Turkey, Saudi Arabia, the Czech Republic, Spain, Germany, India, China, Egypt, Slovenia, Greece, and Italy. In the present study, we evaluated the data of 4,153 COVID-19 patients and 5,229 healthy individuals.

3.3. The rs4646994 polymorphism and susceptibility to COVID-19

The frequency of D and I alleles in patients infected with SARS-CoV-2 was measured at 66.7% (95% CI: 57.8–74.5; I^2: 89.19; *p* value: 0.01; Begg's *p* value: 0.8; Egger's *p* value: 0.4) and 44.5% (95% CI: 38.6–50.6; I^2: 94.34; *p* value: 0.01; Begg's *p* value: 0.18; Egger's *p* value: 0.20), respectively. In addition, the distribution of DD, ID, and II genotypes in COVID-19 patients was 35.8% (95% CI: 22.6–51.6; I^2: 89.19; *p* value: 0.05; Begg's *p* value: 0.1; Egger's *p* value: 0.2), 28.9% (95% CI: 14.3–49.9; I^2: 92.11; *p* value: 0.01; Begg's *p* value: 0.14; Egger's *p* value: 0.07), and 10.1% (95% CI: 4.9–19.7; I^2: 77.15; *p* value: 0.04; Begg's *p* value: 0.18; Egger's *p* value: 0.01), respectively.

Our analysis showed that individuals with the D allele and DD genotype are significantly more at risk of contracting COVID-19 (Table 2). Furthermore, in subgroup analysis, we found that the rs4646994 DD genotype significantly increases the risk of COVID-19 in the Asian population (OR: 1.75; 95% CI: 1.11–2.76; *p* value: 0.01), whereas, this was not the case in the Western population (OR: 1.36; 95% CI: 0.87–2.12; *p* value: 0.17). Thus, the DD genotype can increase the risk of COVID-19 in the Asian population by 1.7-fold (Fig. 2). Nevertheless, due to small population size, we need further studies to confirm the findings of the present study.

3.4. The rs4646994 polymorphism and severity of SARS-CoV-2 infection

The distribution of D and I alleles in COVID-19 patients with severe clinical outcomes was 52.4% (95% CI: 32.5–71.5; I^2: 93.48; *p* value: 0.01; Begg's *p* value: 0.36; Egger's *p* value: 0.49) and 51.3% (95% CI: 34.3–68.0; I^2: 91.36; *p* value: 0.01; Begg's *p* value: 0.5; Egger's *p* value: 0.36), respectively. Furthermore, the frequency of II, ID, and DD genotypes was measured at 15.5% (95% CI: 9.5–24.3; I^2: 54.92; *p* value: 0.10; Begg's *p* value: 0.04; Egger's *p* value: 0.01), 21.9% (95% CI: 8.1–47.0; I^2:

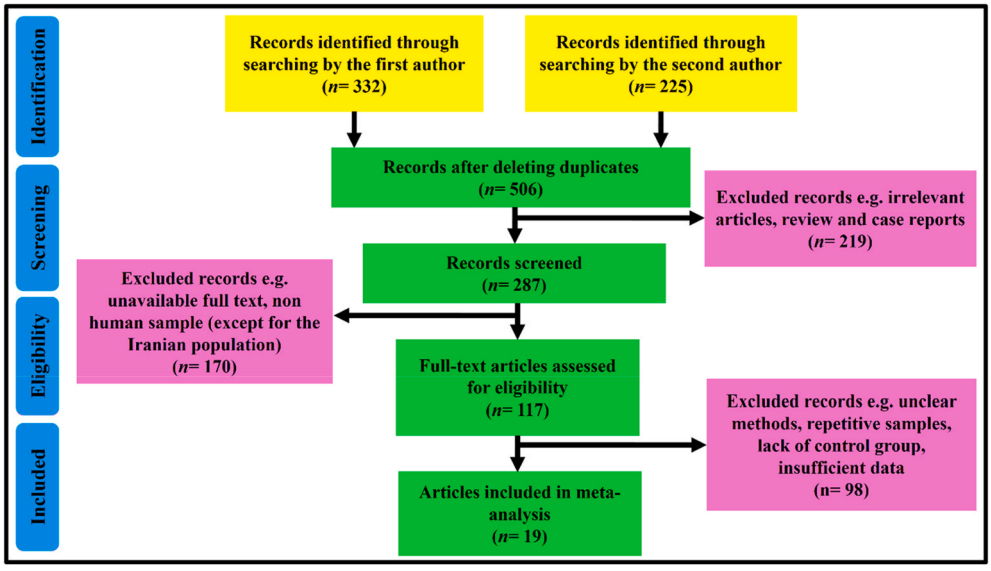

Fig. 1. The flowchart of search strategy for selecting included studies.

93.36; *p* value: 0.01; Begg's *p* value: 0.04; Egger's *p* value: 0.03), and 50.0% (95% CI: 29.4–70.6; I^2: 86.37; *p* value: 0.01; Begg's *p* value: 0.08; Egger's *p* value: 0.03), respectively.

This meta-analysis showed that people with the DD genotype are 3.04-fold more susceptible to severe clinical outcomes of COVID-19 than others, while the risk of severe disease in those with II genotype is ~0.6-fold lower (Table 3). According to the subgroup analysis, although the DD genotype increased the severity of SARS-CoV-2 disease by 2.07-fold in Western countries (OR: 2.07; 95% CI: 1.23–3.49; *p* value: 0.01), no significant relationship was observed in the Asian population (OR: 0.96; 95% CI: 0.55–1.67; *p* value: 0.88). Moreover, the II genotype reduced the risk of severe clinical outcomes by 0.6-fold (OR: 0.63; 95% CI: 0.44–0.89; *p* value: 0.01) in Western countries, whereas this was not the case in Asians. (OR: 0.46; 95% CI: 0.17–1.20; *p* value: 0.1). Therefore, it can be concluded that the DD genotype increases the risk of the severity of disease, while, it seems that the II genotype has a protective role (Fig. 3).

3.5. The rs2285666 polymorphism and susceptibility to SARS-CoV-2 infection

In association with the rs2285666 polymorphism, the allelic variation is G, A, C and T. The frequency of these alleles was as follows: G, 76.4% (95% CI: 22.0–97.4; I^2: 97.17; *p* value: 0.01); A, 23.4% (95% CI: 2.6–77.4; I^2: 97.11; *p* value: 0.01); C, 75.4% (95% CI: 53.8–89.0; I^2: 87.98; *p* value: 0.01); T, 24.6% (95% CI: 1.1–46.2; I^2: 87.98; *p* value: 0.01). In addition, the distribution of genotypes among COVID-19 confirmed cases was also measured as follows: GG, 68.1% (95% CI: 37.5–88.3; I^2: 95.56; *p* value: 0.01; Begg's *p* value: 0.5; Egger's *p* value: 0.76); GA, 14.8% (95% CI: 9.2–23.0; I^2: 63.86; *p* value: 0.01; Begg's *p* value: 0.5; Egger's *p* value: 0.49); AA, 8.1% (95% CI: 1.5–34.4; I^2: 92.95; *p* value: 0.01; Begg's *p* value: 0.5; Egger's *p* value: 0.46); CC, 58.8% (95% CI: 18.8–89.8; I^2: 97.02; *p* value: 0.01); CT, 14.3% (95% CI: 7.9–24.6; I^2: 63.19; *p* value: 0.31); TT, 12.3% (95% CI: 8.5–17.7; I^2: 0.00; *p* value: 0.63).

Our results suggested that there is no meaningful association between the rs2285666 and susceptibility to SARS-CoV-2 infection (Table 4). Finally, in individuals carrying the GG genotype, the risk of SARS-CoV-2 infection increased 1.7-fold, but was not significant (OR: 1.76; 95% CI: 0.48–6.46; *p* value: 0.09).

Table 2
The pooled OR with 95% CI of genetic models of rs4646994 in susceptibility to COVID-19.

Polymorphism (s)	Genetic models	Random-effect models			Heterogeneity	
		OR	95% CI	*p* value	I-squared	*p* value
rs4646994	DD	1.58	1.20–2.08	0.01	6.73	0.36
	ID	0.85	0.48–1.50	0.58	79.39	0.01
	II	0.49	0.21–1.14	0.10	79.61	0.01
	ID + II	0.70	0.43–1.14	0.15	0.00	0.9
	DD + ID	2.29	1.21–4.35	0.01	0.00	0.9
	I	0.82	0.55–1.23	0.34	0.00	0.67
	D	1.72	1.03–2.85	0.03	51.69	0.12

3.6. The rs2285666 polymorphism disease and severity of SARS-CoV-2 infection

In relation to the impact of the rs2285666 polymorphism in the severity of SARS-CoV-2 infection, the frequency of alleles and genotypes was as follows: G allele, 22.4% (95% CI: 14.0–33.9; I^2: 0.00; *p* value: 0.9); A allele, 77.6% (95% CI: 66.1–86.0; I^2: 0.00; *p* value: 0.9); C allele, 69.3% (95% CI: 39.9–88.5; I^2: 93.24; *p* value: 0.01); T allele, 30.7% (95% CI: 11.5–60.1; I^2: 93.24; *p* value: 0.01); GG genotype, 88.0% (95% CI: 80.0–93.1; I^2: 0.00; *p* value: 0.01); GA genotype, 4.5% (95% CI: 1.1–16.4; I^2: 0.00; *p* value: 0.9); AA genotype, 6.8% (95% CI: 2.2–19.1; I^2: 0.00; *p* value: 0.9); CC genotype, 52.2% (95% CI: 44.0–60.3; I^2: 29.10; *p* value: 0.23); CT genotype 22.8% (95% CI: 14.9–33.4; I^2: 59.57; *p* value: 0.1); TT genotype, 20.9% (95% CI: 13.9–30.1; I^2: 50.29; *p* value: 0.15). The present meta-analysis showed that in people harboring the GG and TT genotypes, the risk of severe COVID-19 infection was very high, while it seems that the risk of severe disease is low in people with other genotypes such as GA, AA, and CC (Table 5). However, further investigation need to validate the present finding.

3.7. Publication bias

According to the measurements based on Begg's *p* value test and Egger's *p* value test, a significant publication bias was observed in some cases. In particular, the analytical detection of asymmetry in the funnel plot also confirmed this publication bias (Fig. 4).

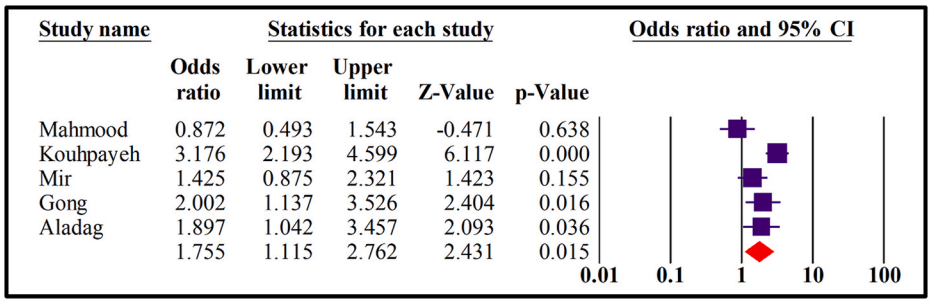

Fig. 2. The forest plot associated with the frequency of the DD genotype and the risk of COVID-19 in the Asian population.

Table 3
The pooled OR with 95% CI of genetic models of rs4646994 in severe clinical outcomes of COVID-19.

Polymorphisms	Genetic Models	Random-effect models			Heterogeneity	
		OR	95%CI	*p* value	I-squared	*p* value
rs4646994	DD	3.04	0.98–9.42	0.05	70.91	0.03
	ID	0.51	0.07–3.47	0.49	80.88	0.02
	II	0.59	0.42–0.82	0.02	0.00	0.59
	ID + II	1.08	0.62–1.89	0.77	0.00	0.99
	DD + ID	2.16	0.83–5.61	0.11	0.00	0.99
	I	0.84	0.62–1.12	0.24	0.00	0.41
	D	1.23	0.91–1.64	0.16	0.00	0.46

4. Discussion

SARS-CoV-2 is considered as one of the highly contagious viruses [49]. This virus binds to ACE2 via the receptor-binding domain (RBD) in its spike glycoprotein and then enters human cells [50]. The mechanism of ACE2 binding in SARS-CoV-2 is quite similar to SARS-CoV-1, but affinity for ACE2 in SARS-CoV-2 is significantly higher than in SARS-CoV-1 [51].

As far as we know, this is the first comprehensive meta-analysis that investigated the polymorphisms of RAAS during the pathogenesis of SARS-CoV-2. Our results suggested that rs4646994 and rs2285666 variations can influence the results of susceptibility as well as progression to the acute respiratory distress depending on patient's ethnicity. The rs4646994 DD-genotype could significantly increase the risk of SARS-CoV-2 infection by approximately 1.7-fold in the Asian populations; otherwise, the rs2285666 GG genotype can increase the risk of ARDS in the Western hemisphere.

According to the literature, the imbalance between ACE1 and ACE2 plays a decisive role in the pathogenesis of SARS-CoV-2 [52–54]. The ACE2 receptor counteracts against the proinflammatory and profibrotic effects of Ang-2 by converting it to Ang-(1-7) [34]. Studies show that increased levels of Ang-2 cause severe injury to lung and heart tissues, but in people carrying the rs2285666 A-allele, due to the expression of high levels of ACE2, they are usually protected against the ACE1/ACE2 imbalance [55,56]. Based on studies, the severity of COVID-19 in patients can be associated with several underlying conditions such as coronary artery disease (CAD), male sex, age over 60 years, obesity, diabetes mellitus (DM), and hypertension [57]. Comprehensive studies on the Mexican population showed that I/D polymorphism of *ACE* gene is a genetic marker for susceptibility to complications such as CVD,

Table 4
The pooled OR with 95% CI of genetic models of rs2285666 in susceptibility to COVID-19 infection.

Polymorphisms	Genetic models	Random-effect models			Heterogeneity	
		OR	95% CI	*p* value	I-squared	*p* value
rs2285666	GG	1.76	0.48–6.46	0.39	91.99	0.01
	GA	0.56	0.21–1.51	0.25	82.21	0.04
	AA	0.76	0.15–3.83	0.74	77.61	0.01
	CC	1.04	0.53–2.04	0.86	0.00	0.9
	CT	0.68	0.29–1.61	0.39	0.00	0.9
	TT	1.41	0.54–3.64	0.47	0.00	0.9
	G	1.59	0.13–18.68	0.7	95.17	0.01
	A	0.61	0.05–6.82	0.6	94.94	0.01
	C	0.92	0.43–1.96	0.83	0.00	0.9
	T	1.27	0.58–2.79	0.53	0.00	0.9

Table 5
The pooled OR with 95% CI of genetic models of rs2285666 in severe clinical outcomes of COVID-19.

Polymorphisms	Genetic Models	Random-effect models			Heterogeneity	
		OR	95% CI	*p* value	I-squared	*p* value
rs2285666	GG	4.88	2.78–8.56	0.01	0.00	0.8
	GA	0.22	0.11–0.42	0.01	0.00	0.5
	AA	0.31	0.13–0.78	0.01	0.00	0.3
	CC	0.35	0.19–0.66	0.01	0.00	0.9
	CT	1.31	0.61–2.80	0.47	0.00	0.9
	TT	3.83	1.64–8.91	0.02	0.00	0.9
	G	1.50	0.89–2.55	0.12	93.76	0.01
	A	2.92	0.83–10.18	0.09	81.47	0.02
	C	0.34	0.17–0.67	0.02	0.00	0.9
	T	3.43	1.68–6.97	0.01	0.00	0.9

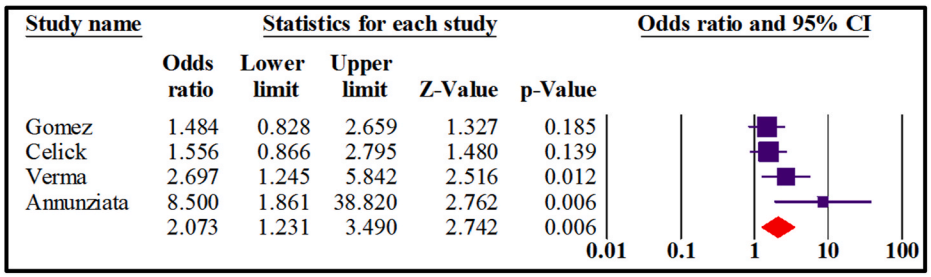

Fig. 3. The forest plot of the role of DD and II genotypes in the severity of COVID-19.

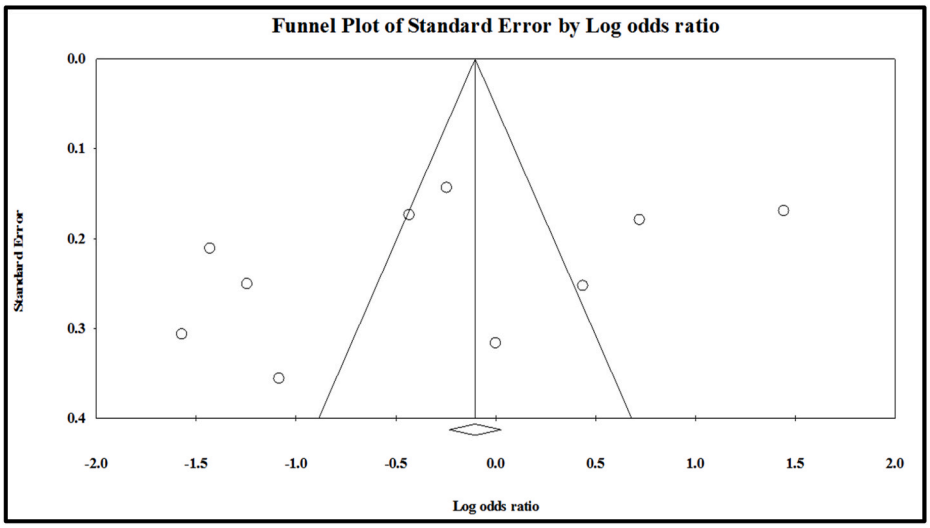

Fig. 4. The asymmetry of funnel plot associated with included studies.

diabetes, and hypertension [58,59]. Individuals harboring polymorphisms in a variety of genes e.g. ACE1, ACE2, TMPRSS2, HLA, CD147, MIF, IFNG, IL6, and IFITM3 are commonly involved in the outcomes of SARS-CoV-2 and other pathogenic coronaviruses [60,61].

In the present study, we analyzed the impact of polymorphisms of ACE1 and ACE2 on the severity of COVID-19. According to our findings, the frequency of D and I alleles in patients infected with SARS-CoV-2 was at 66.7% and 44.5%, respectively. Using subgroup analysis, we found that unlike the Western population, the Asian population carrying rs4646994 DD genotype is significantly susceptible to infection by SARS-CoV-2. On the other hand, based on the results of subgroup analysis, the rs4646994 DD genotype increases the risk of the severity of COVID-19 in patients, but it seems that the II genotype is more resistant to the severity of COVID-19. Regarding the rs2285666 polymorphism, our results revealed that the rs2285666 AA genotype was associated with the non-significant increase in the risk of SARS-CoV-2 infection. On the other hand, in current meta-analysis we realized that in people possessing the rs2285666 GG genotype, the risk of progression to severe infection is high, while, the rs2285666 GA genotype has a protective role in patients against severe COVID-19.

In a study by Mir et al., they found that the ACE1-DD genotype was associated with the severity of COVID-19, while the ACE1-II genotype played a protective role against the development of severe COVID-19 infection; as well as, their study on the ACE2-DD genotype showed that this genotype was strongly associated with increased COVID-19 mortality [32].

Contrary to our results, Celik et al. in their cohort study on 155 patients did not observed a significant relationship between two polymorphisms rs2106809 and rs2285666 with the clinical outcomes of COVID-19 [31]. On the other hand, Srivastava et al. observed a positive correlation between rs2285666 polymorphism and low mortality rate among the Indian population [62].

Verma et al. suggested that the severity of the COVID-19 in patients depends on the rs4646994 DD genotype in addition to age, diabetes, and hypertension35]]. Based on studies, the frequency of the D allele can be associated with the racial differences; in fact, the higher frequency of the D allele in African-American and European countries infected with SARS-CoV-2 seems to be associated with higher mortality compared to Indians, Asians, and White people [63,64].

Based on our meta-analysis, rs4646994 and rs2285666 polymorphisms are actively involved in the pathogenesis of SARS-CoV-2 infection. It seems that these polymorphisms act as biomarkers for susceptibility to SARS-CoV-2 in Asian population (rs4646994), as well as the development of acute respiratory distress syndrome in Western countries (rs2285666). However, our study had several limitations including: 1) small sample size; 2) low number of included studies; 3) considerable heterogeneity and publication bias; 4) failure to investigate the role of underlying diseases in the severity of COVID-19 due to lack of access to raw data. Therefore, the results should be interpreted with more caution. Further prospective studies should be considered to confirm the present findings.

5. Conclusion

There is ample evidence that RAAS plays a role in the pathogenesis of SARS-CoV-2. According to the literature, RAAS increases the risk of hypertension, diabetes, CVD, which in turn play a crucial role in the clinical outcomes of SARS-CoV-2 infection. Our meta-analysis showed that rs4646994 and rs2285666 polymorphisms could be considered as two potential biomarkers for the diagnosis of susceptibility to COVID-19 as well as the severe clinical outcomes of SARS-CoV-2. We first proposed that these polymorphisms could be helpful in predicting pathogenesis of SARS-CoV-2. The rs4646994 DD genotype increases the risk of susceptibility to COVID-19 by approximately 1.7-fold in the Asian populations, whereas, the rs2285666 GG genotype can increase the risk of ARDS in Western patients. In addition, the rs2285666 GA genotype plays a protective role against ARDS. Finally, further studies with larger populations are needed to confirm the present findings.

CRediT authorship contribution statement

Masoud Keikha: Writing – original draft, Formal analysis. **Mohsen Karbalaei:** Writing – review & editing.

Declaration of competing interest

Formally, we confirm, there are not conflict of interest.

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