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Association between the ACE I/D Variant and COVID-19 Susceptibility and Severity; a Meta-Analysis

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ABSTRACT

Aims Several studies investigated the association of ACE I/D polymorphism with the risk and severity of COVID-19 infection. However, the information in each of the published studies is limited, and the results were inconsistent or even contradictory. Accordingly, this meta-analysis evaluated the association between ACE I/D polymorphism and COVID-19 susceptibility and severity.

Materials & Methods Two investigators independently searched the PubMed, Embase, Google Scholar, Scopus, and Science Direct databases. Five studies including 1029 cases and 3561 controls were retrieved to evaluate the association between ACE I/D polymorphism and the risk of COVID-19. Furthermore, a meta-analysis of the correlation between the ACE I/D variant and the severity of infection covered 5 case-control studies, including 264 sever-cases and 447 mild cases.

Findings There was no association between the ACE I/D variant in all genetic models and COVID-19 susceptibility. However, our analysis revealed that there was a significant association between ACE I/D variant in the allele contrast (95% CI=0.5291-0.8353; p<0.001), recessive (95% CI=0.4268-0.9172; p=0.01) and dominant (95% CI=0.3974-0.8092; p=0.001) models and severity of COVID-19.

Conclusion ACE I/D polymorphism is associated with the severity of COVID-19 infection. There is no association between the ACE I/D variant in all genetic models and COVID-19 susceptibility.

Keywords ACE; I/D Polymorphism; COVID-19; Meta-Analysis

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Introduction

Coronaviruses (CoVs) belong to the subfamily Coronavirinae and the family Coronaviridae, which are coated RNA viruses containing a non-segmented single-stranded positive-sense RNA. This family is divided into four genera including alpha, beta, delta, and, gamma CoVs [1]. CoVs have been the cause of two epidemics over the past twenty years including acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) [2-4]. At the end of December 2019, the Wuhan Municipal Health Commission reported the outbreak of new viral pneumonia named a novel CoV (COVID-19) by the World Health Organization (WHO) in January 2020 [5]. According to the WHO data, more than 276 million cases of COVID-19 have been recorded worldwide, including at least 6,667,000 deaths until December 2022.

It has been reported that the Renin-Angiotensin-Aldosterone System (RAAS) plays an important role in the pathogenesis of COVID-19 [6]. The angiotensin-converting enzyme (ACE) is the main part of the RAAS that is involved in coronavirus infection. ACE is the major receptor for viral entry of COVID-19 in humans. It has been suggested that pathogenic COVID-19 spike (S) glycoprotein binds via its receptor-binding domain (RDB) with a high affinity to its target cells through human ACE [7]. The binding and the subsequent cell entry of COVID-19 lead to reduce expression of cellular ACE [8]. Clinical studies have revealed that ACE insertion/deletion (I/D) polymorphism (rs4646994, rs1799752) could be associated with the ACE circulating and tissue levels and thereby, the severity of COVID-19 infection in humans [9, 10].

ACE rs4646994 variant is characterized by the insertion (*I*) or deletion (*D*) of a 287-bp Alu repeat sequence in intron 16 of the ACE gene [8]. Several studies evaluated the association of the ACE rs4646994 variant with the risk and severity of COVID-19 infection [11-13]. However, the information in each of the published studies is limited, and the results were inconsistent or even contradictory. Accordingly, this meta-analysis aimed to investigate the association between ACE I/D polymorphism and COVID-19 susceptibility and severity.

Materials and Methods

Search strategy and selection criteria

We performed a search on PubMed, Embase, Google Scholar, Scopus, and Science Direct databases, for papers published in English up to December 2022, using a combination of keywords "insertion/deletion (I/D)", "rs4646994", "rs1799752", "ACE polymorphism", "COVID-19", and "SARS-CoV-2". Original case-control studies that reported data relevant to ACE gene I/D polymorphism and the risk and severity of COVID-19, mentioned the sufficient genotype data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs), categorized COVID-19 patients as severe and mild groups were eligible for this meta-analysis. Furthermore, studies lacking case-control evaluation of the association between ACE I/D polymorphism and risk and severity of COVID-19, genotype distribution not consistent with Hardy–Weinberg equilibrium (HWE), case report studies, meta-analysis, reviews, abstract or conference papers were excluded.

Data extraction and statistical analysis

The required data were retrieved by two independent investigators from the full-text eligible articles and the consensus was achieved by a third reviewer. Moreover, conflicting articles of interest and any disagreement were resolved by a team discussion. The following data were extracted from the selected studies: author name, year, sample size, ethnicity, and country.

The meta-analysis was performed as stated by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [14]. All analyses were performed using the Web tool MetaGenyo, Version 12.0 [15]. MetaGenyo combines the effect sizes of the included studies by weighting the data according to the amount of information in each study. Heterogeneity between trials was evaluated using Cochrane's Q statistic and the I^2 test and considered significant at $I^2 > 50\%$ or $p<0.1$. Accordingly, in case of low heterogeneity, the fixed effects model and otherwise, the random effect model were applied to combine the studies. Forest plots were applied to summarize information for effect size and the corresponding 95% confidence interval (CI) of each study and the pooled effect. Sensitivity analyses were performed by removing one study at a time to evaluate the consistency of the results. Moreover, Funnel plots and Begger's and Egger's tests were used to evaluate publication bias.

Findings

Association of the ACE I/D variant and COVID-19 susceptibility

After a literature search of PubMed, Embase, and Scopus, 7 studies were retrieved to the evaluation of the association between ACE I/D polymorphism and the risk of COVID-19 infection. Among these five papers met our inclusion criteria including 1029 cases and 3561 controls. The two studies were excluded for being against the HWE. There were two studies of Iran, one of Asturias, one of Italy, and one of Czech (Table 1).

Four genetic models including allele contrast (I vs. D), recessive (II vs. ID and DD), dominant (II+ID vs. DD), and over-dominant (ID vs. II+DD) were used to compare the genotypes and alleles. Since there was heterogeneity across the studies, the random effect model was applied to evaluate the odds ratio ($I^{\wedge 2} > 50$; $p<0.05$). Our analysis indicated that there was no association between the ACE I/D variant in the allele

contrast (95% CI=0.5252-1.1994; p=0.27), recessive (95% CI=0.2763-1.0964; p=0.08), dominant (95% CI=0.4776-1.6531; p=0.7), and over-dominant (95% CI=0.6659-1.8827; p=0.66) models and COVID-19 susceptibility (Figure 1). The funnel plot and Egger's test were applied to evaluate the publication bias of the individual studies. There was no significant publication bias according to the funnel plot and Egger's test (p>0.05) for all the genetic models. Moreover, sensitivity analysis was performed to examine the impact of the individual data on the pooled ORs. After each study was excluded from the current meta-analysis, there was no significant shift or change in the level of significance and odds ratio. This analysis indicated our results were statistically robust.

Table 1) Characteristics of the investigated studies (all 2020) of the association of the rs4646994 polymorphism and risk of COVID-19 infection

Study	Country	Cases/ Controls	Case Subjects			Control Subjects			HW-p Value
			II	ID	DD	II	ID	DD	
Juan Gómez [23]	Asturias	204/536	22	107	75	85	256	195	0.94
Cecilia Calabrese [24]	Italy	68/111	5	25	38	13	50	48	0.9
Jaroslav A. Hubacek [13]	Czech	408/2579	107	210	91	547	1331	701	0.06
Mohammadarian Akbari [31]	Iran	91/91	4	70	17	21	37	33	0.10
Hamid Reza Kouhpayeh [11]	Iran	258/244	25	89	144	51	123	70	0.82

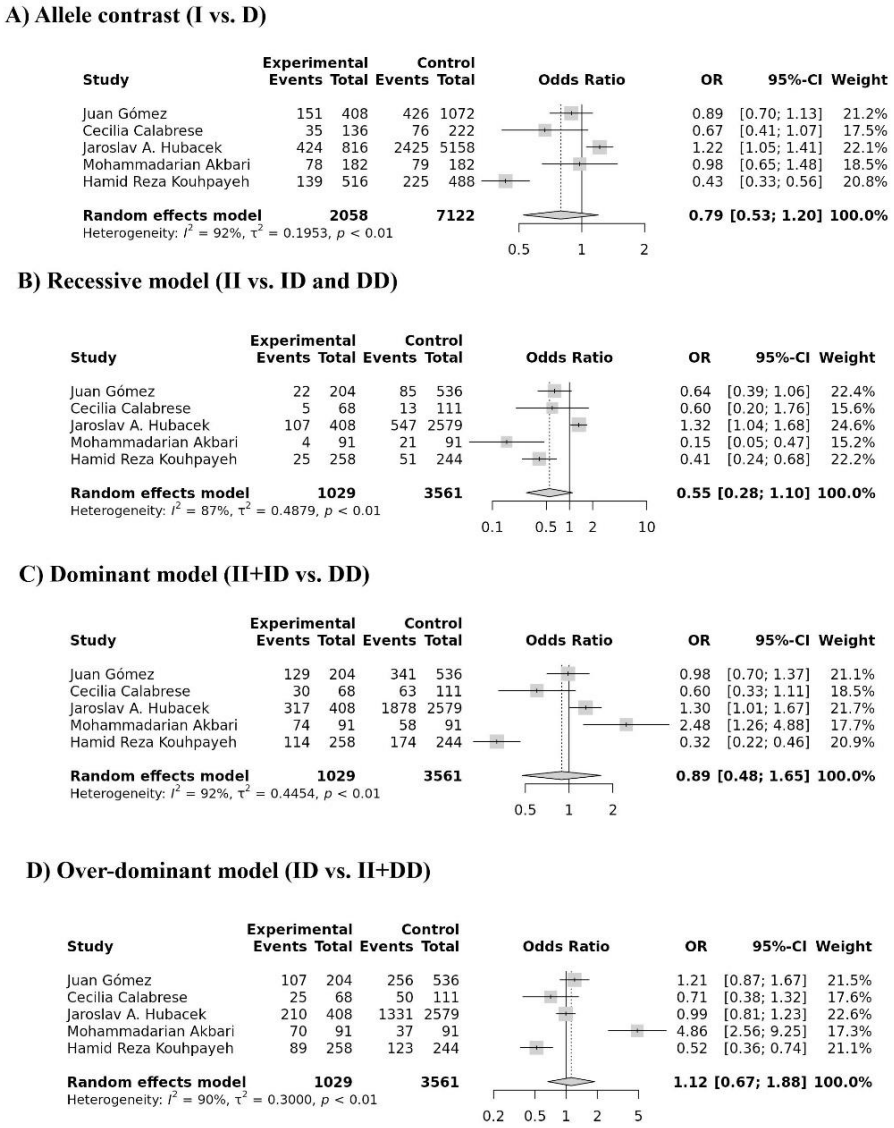

Figure 1) Forest plot of the association between the rs4646994 polymorphism and risk of COVID-19 infection. A) allele contrast (I vs. D), B) Recessive model (II vs. ID and DD), C) Dominant model (II+ID vs. DD) and D) Over-dominant model (ID vs. II+DD). Boxes illustrate the effect size for each sample in the analysis; the size of the boxes shows the weighting for each study and lines represent the .95 confidence interval for each effect size. The diamond represents the overall effect of the meta-analysis.

Association between the ACE I/D polymorphism and severity of COVID-19 infection

For the evaluation of the association between the ACE I/D variant and the severity of COVID-19 infection, 10 studies were retrieved. Among these, five papers met our inclusion criteria, including 264 severe and 447 mild cases. Two studies were not consistent with HWE and 3 investigations were rejected because they did not categorize patients as mild or severe subgroups. Study regions comprised Turkey, India, and Asturias (Table 2).

The association between the ACE I/D polymorphism and severity of COVID-19 infection was evaluated in four genetic models including allele contrast (I vs. D), recessive (II vs. ID and DD), dominant (II+ID vs. DD) and over-dominant (ID vs. II+DD). Based on heterogeneity, a fixed (I^2<50; p>0.05) or random (I^2>50; p<0.05) effect model was applied to evaluate the odds ratio. Our analysis revealed that there was a significant association between the ACE I/D variant in the allele contrast (95% CI=0.5291-0.8353; p<0.001), recessive (95% CI=0.4268- 0.9172; p=0.01) and dominant (95% CI=0.3974-0.8092; p=0.001) models and severity COVID-19 susceptibility (Figure 2). We did not observe a significant association for the over-dominant model (95% CI=0.4916-1.6977; p=0.77). These findings suggested that ACE- I allele is associated with an increase in COVID-19 infection severity. The funnel plot and Egger's test were applied to evaluate the publication bias of the individual studies. The results showed no publication bias in this meta-analysis except for over-dominant. Furthermore, Sensitivity analysis was performed to estimate the impact of the individual data set on the pooled ORs. There was no significant shift or change in the level of significance and odds ratio after removing each study from the current meta-analysis.

Table 2) Characteristics of the investigated studies (all 2020) of the association of the rs4646994 polymorphism and severity of COVID-19 infection

Study	Country	Severe/Mild Cases	Severe Cases			Mild Cases			HW-p Value
			II	ID	DD	II	ID	DD	
Juan Gómez [23]	Asturias	67/137	5	31	31	17	76	44	0.17
Elifcan Aladag [10]	Turkey	12/53	0	10	2	8	22	23	0.59
Sushma Verma [12]	India	120/149	42	48	30	74	58	17	0.47
Sevim Karakaş Çelik [32]	Turkey	35/78	6	15	14	17	37	24	0.70
Ozgur Gunal [33]	Turkey	30/30	9	2	19	7	8	15	0.09

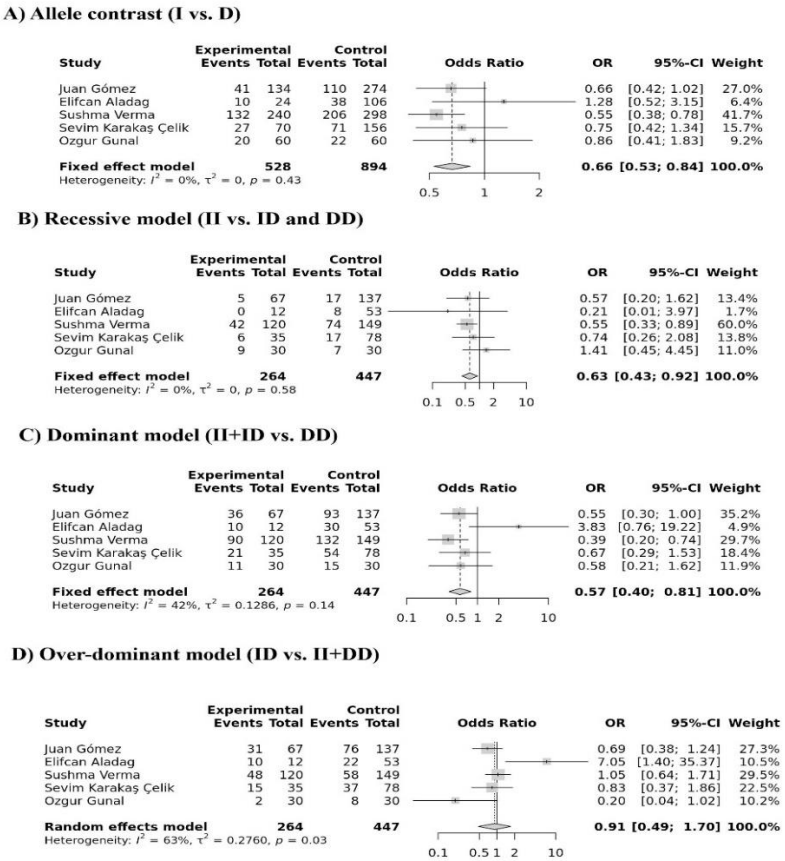

Figure 2) Forest plot of the association between the rs4646994 polymorphism and severity of COVID-19 infection. A) Allele contrast (I vs. D), B) Recessive model (II vs. ID and DD), C) Dominant model (II+ID vs. DD) and D) Over-dominant model (ID vs. II+DD). Boxes illustrate the effect size for each sample in the analysis; the size of the boxes shows the weighting for each study and lines represent the .95 confidence interval for each effect size. The diamond represents the overall effect of the meta-analysis.

Discussion

COVID-19 is known as the most challenging problem around the world today that is associated with a high mortality rate mainly in cases with underlying diseases such as diabetes and hypertension [16, 17]. ACE catalyzes the synthesis of Angiotensin-II (Ang-II) from Ang-I that binds to the AT1-receptor inducing vasoconstriction, fibrosis, inflammation, and, thrombosis [18, 19]. ACE act as a surface receptor of SARS-CoV-2, catalysis the conversion of AngII to angiotensin 1–t known as AngII antagonist [20]. Binding SARS-CoV-2 to ACE2 is accompanied by ACE/ACE2 imbalance and ultimately led to an increase in AngII level as well as its deleterious effects, especially in lung tissue [21, 22]. Therefore, functional variants of ACE may be associated with the susceptibility and severity of SARS-CoV-2 infection.

In the present study, ACE rs4646994 polymorphism is not associated with susceptibility to COVID-19. However, our findings suggested a significant negative association between the ACE rs4646994-I allele and the severity of COVID-19 infection. Previous studies have described that the rs4646994 D allele causes an increase in ACE/AngII levels and is therefore involved in microvascular permeability and pulmonary edema [9, 23]. In a study released by Gómez *et al*. the distribution of the DD genotype between COVID-19 patients and controls was not statistically significant [23]. Another study demonstrated that in patients with COVID-19, the prevalence of the DI genotype and D allele is significantly higher than that in controls [10]. In this context, it has been reported that in COVID-19 patients with pulmonary embolism, the prevalence of the DD genotype is considerably higher than in those without thromboembolic complications [24]. In contrast to the mentioned reports, Hubacek *et al*. presented the II genotype as a deleterious marker [13]. Few published meta-analyses evaluated the ACE variant associations with Acute respiratory distress syndrome (ARDS). Inconsistent with our findings, Akihisa Matsuda *et al*. reported that there are no associations for any genetic model [25]. However, other studies showed a significant association of the DD rs4646994 with ARDS at least in one genetic model [26, 27]. It is necessary to mention that, these meta-analyses were performed before the COVID-19 pandemic, and evaluated the association of ACE I/D polymorphism with ARDS.

Data analysis in the present study provided a negative correlation between the rs4646994 I allele and the severity of COVID-19 infection. Several experimental studies evaluated the association between ARDS and the severity of COVID-19 infection. In this regard, it has been reported that the I allele act as a protective factor against the prevalence of SARS-CoV-2 infection and its complications [11]. An epidemiological study in the Asian population by Pati *et al*. also showed a considerably positive correlation between the frequency of the D allele and the frequency of COVID-19/million [28]. However, the conclusions were controversial. Accordingly, in this meta-analysis, the association between the ACE-rs4646994 polymorphism and the severity of COVID-19 infection was evaluated in four different genetic models. Our analysis revealed that there was an association between the rs4646994 variant in the allele contrast, recessive, and dominant models and COVID-19 severity. One published meta-analysis evaluated the association of the ACE I/D variant with the severity of COVID-19 infection, not disease risk [29]. In line with our findings, they showed that the DD genotype may confer an increased risk of severe COVID-19. However, our study had a distinct difference from their study. Unlike them, we excluded the Calabrese *et al*. [24] study from our analysis. This study did not categorize patients into severe and mild groups. Accordingly, we analyzed the data from the Aladag *et al*. [10] instead of the Calabrese *et al*.

Considering the role of the ACE I/D polymorphism in the severity of COVID-19, identifying this polymorphism in COVID-19 patients can recognize those who are prone to the complications of COVID-19 and these patients should be given special attention in care management in the clinical environment. Also, by making these patients aware of the role of this polymorphism and vulnerability, they should be advised to follow the safety protocol against COVID-19.

Even though the researchers tried to do a well-designed and robust meta-analysis, that there are some limitations should be acknowledged. First, only a small number of studies were relevant to this meta-analysis. Second, due to low ethnic diversity, we couldn't perform subgroup analysis. Third, we had insufficient data to conduct an association between rs4646994 polymorphism and COVID-19-related pathogen factors. Nevertheless, this study is limited in its small number of included studies and should be interpreted cautiously. Further study is still required to confirm the association in different populations.

Conclusion

ACE I/D polymorphism is associated with the severity of COVID-19 infection. However, there is no association between the ACE I/D variant in all genetic models and COVID-19 susceptibility.

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Ethical Permissions: The study was approved by the Yasuj University of Medical Sciences Ethics Committee (IR.YUMS.REC.1399.004).

Conflicts of Interests: The authors declare that they have no conflict of interest.

Authors' Contribution: Nikooei Sh (First Author), Main Researcher/Introduction Writer/Discussion Writer (30%); Ghasemi H (Second Author), Assistant Researcher/Statistical Analyst (20%); Zarei MR (Third Author), Introduction Writer/Methodologist (10%);

Vakilpour H (Forth Author), Assistant Researcher/Statistical Analyst (10%); Alipoor B (Fifth Author), Main Researcher/Statistical Analyst (30%)

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