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Article

Asociation of ACE I/D and TNF- α -308 Polymorphisms with COVID-19 Severity in a Mexican Population

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Abstract

Background: COVID-19 severity shows marked interindividual variability, suggesting a role for host genetic factors. Polymorphisms in genes involved in the renin–angiotensin system and inflammatory response, such as the angiotensin-converting enzyme (ACE) and the tumor necrosis factor- α (TNF- α), have been proposed as potential modulators of disease severity. **Objectives:** To evaluate the association between the ACE I/D (rs4646994) and TNF- α -308 G/A (rs1800629) polymorphisms and COVID-19 severity in a Mexican population. **Methods:** A total of 236 individuals with RT-PCR–confirmed SARS-CoV-2 infection were included. Patients were classified as hospitalized (severe, n = 155) or non-hospitalized (asymptomatic–mild, n = 81). Genotyping was performed by PCR–RFLP. Genotype distributions were analyzed using χ^2 tests under dominant and recessive genetic models, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. **Results:** The ACE I/D polymorphism showed a significant association with COVID-19 severity. Carriers of the I allele (ID + II) had a higher risk of hospitalization compared with DD homozygotes (OR = 2.78, 95% CI: 1.53–5.06, p = 0.001). Sex-stratified analysis revealed that this association was significant only in male patients. No significant association was observed between the TNF- α -308 G/A polymorphism and disease severity. **Conclusions:** The ACE I/D polymorphism is associated with COVID-19 severity in a Mexican population, with a stronger effect observed in males. These findings underscore the relevance of host genetic background and sex-specific effects in COVID-19 outcomes. Further studies including larger cohorts, healthy controls, and multivariable analyses are required to confirm these associations.

Keywords: COVID-19; ACE I/D polymorphism; TNF- α -308 G/A; disease severity; Mexican population

1. Introduction

Since late 2019, coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has posed a major global public health challenge [1, 2]. Although, most infected individuals developed mild to moderate symptoms, a significant proportion progress to severe disease characterized by respiratory failure, systemic inflammation, coagulopathy, and increased mortality [3–7]. The clinical course of COVID-19 is highly heterogeneous and influenced by multiple factors, including advanced age, male sex, obesity, smoking and comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, and cancer [5, 8, 9]. Beyond these

well-established risk factors, host genetic variability has emerged as a key determinant of susceptibility and disease severity [9, 10].

Several investigations have correlated the presence of polymorphisms of some genes with the severity of the disease; in these investigations, the genetic variants influence the progression and outcome of the subjects with SARS-CoV-2 infection [10-12]. Genome-wide association studies (GWAS) and candidate gene approaches have identified several genetic associated with severe COVID-19, including the 3p21.31 locus, with population-specific effects [10, 13]. Among the most extensively studied genes is the ACE pathways, which plays a central role in cardiovascular homeostasis and inflammatory regulation [11, 14, 15]. ACE-1 catalyzes the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, whereas ACE-2 counterbalances this effect by converting angiotensin II to angiotensin [15-17]. Importantly, ACE-2 also serves as the primary cellular receptor for SARS-CoV-2, facilitating viral entry into host cells [16, 17]. ACE-2 is expressed in multiple tissues including lungs, intestine, and heart, and its dysregulation during infection contributes to endothelial dysfunction, inflammation, and thrombotic complications observed in severe COVID-19 cases [17, 18]. In parallel, excessive inflammatory responses play a critical role in COVID-19 pathogenesis [7, 19, 20]. Severe cases are often marked by a cytokine storm characterized by elevated levels of pro-inflammatory mediators, including TNF- α , interleukins (IL-1, IL-6, IL-8), and other cytokines [20].

The polymorphism in these genes has been associated with several diseases like diabetes and hypertension and now with the progression and severity of COVID-19 disease [18, 19]. Genetic polymorphisms within the ACE gene, particularly the insertion/deletion (I/D) variant (rs4646994), have been associated with altered ACE activity and have been implicated in cardiovascular and metabolic diseases [16, 18, 21, 22]. Several studies have suggested a relationship between the ACE I/D polymorphism and COVID-19 severity or mortality; however, results remain inconsistent across populations [21, 22]. On the other hand, TNF- α -308 G/A polymorphism (rs1800629) has been associated with increased transcriptional activity of the TNF- α gene and with susceptibility to inflammatory, metabolic, and infectious diseases [23, 24]. Recent evidence suggests that this polymorphism may influence COVID-19 severity by modulating the host inflammatory response. Despite growing evidence linking ACE and TNF- α polymorphisms to COVID-19 outcomes, data regarding their combined impact in Latin American populations, particularly in Mexico, remain scarce. Therefore, the aim of this study was to evaluate the association between the ACE I/D (rs4646994) and TNF- α -308 G/A (rs1800629) polymorphisms and COVID-19 severity in a Mexican population.

2. Materials and Methods

A total of 236 subjects with confirmed SARS-Cov-2 infection by reverse transcription-polymerase chain reaction (RT-PCR) were included in the study. Participants were recruited between 2020 and 2021 and were all native residents of Saltillo, Coahuila, México. The study was divided into two groups according to disease severity. The severe group consisted of 155 hospitalized patients admitted to the COVID-19 unit of the Instituto Mexicano del Seguro Social (IMSS) No. 2 Hospital. Severity classification was based on the Mexican Clinical Guide for Treatment of COVID-19 and included the presence of pneumonia, respiratory rate >30 breaths per minute, oxygen saturation below than 90%, and/or acute respiratory failure, among other criteria [25]. The non-severe group included 81 non-hospitalized individuals with asymptomatic or mild COVID-19, who did not present any of the aforementioned clinical features. All participants provided written informed consent to enrollment. Blood samples were collected before the initiation of national COVID-19 vaccination program; therefore, none of the participants had received SARS-CoV-2 vaccination at the time of sampling. The study protocol was approved by the Research Ethics Committee of the General Hospital Saltillo (approval number 17/2023) and conducted in accordance with the ethical principles of the Declaration of Helsinki.

DNA extraction and Genotyping

Genomic DNA was extracted from peripheral blood samples using the phenol-chloroform method and precipitated with ethanol. DNA pellets were resuspended in sterile distilled water at a final concentration of 100 ng/μl and stored at -20°C until analysis. Genotyping of the ACE insertion/deletion (I/D) polymorphisms (rs4646994) was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis, following a previously described protocol with minor modifications [26]. PCR amplification was carried out in a final reaction volume of 25 μL containing 500 ng of genomic DNA, 0.2 mM dNTPs, 2 mM MgCl₂, 0.5 μM primers (IDT, Coralville, Iowa, USA), 2.5 U Taq DNA Polymerase (Invitrogen TM, Brazil) and reaction buffer. The primer sequences were as follows: primers forward 5'-CTGGAGACCACTCCCATCCTTTCT-3' and reverse 5'-ATCTGACGAATGTGATGGCCAC-3'. PCR condition consisted of 35 cycles at 94°C for 1 min, 58°C for 1 min, and 72°C for 1 min. PCR products were separated by electrophoresis on a 1.5% agarose gel stained with ethidium bromide and visualized under ultraviolet light using UVP 2UV High-Performance Transilluminator (Upland, CA, USA) coupled to a KODAK Gel Logic 112/212 Imaging Systems using the Carestream Molecular Imaging software [27].

Genotyping of the TNF-α -308G/A polymorphism (rs1800629) was performed by PCR-RFLP as previously describe with modifications [28]. PCR reaction (25 μL) contained 500 ng of genomic DNA, 0.2 mM dNTPs, 1.5 mM MgCl₂, 0.5 μM of each primer (IDT, Coralville, Iowa, USA), and 2.5 U Taq DNA Polymerase (Invitrogen TM, Brazil). Primers sequences were: forward 5'-GGGACACACAAGCATCAAGG-3', and reverse 5'-AATAGGTTTTGAGGGCCATG-3'. Amplification conditions consisted of 35 cycles at 94°C for 30 s, 61°C for 30 s, and 72°C for 30 s. Approximately 0.5 μg of PCR product was digested overnight at 37°C with NcoI enzyme restriction (New England Biolabs) at 37°C. Digested fragments were separated on 2.5% agarose gel electrophoresis, stained with ethidium bromide, and visualized under ultraviolet light using UVP 2UV High-Performance Transilluminator (Upland, CA, USA) coupled to a KODAK Gel Logic 112/212 Imaging Systems using the Carestream Molecular Imaging software [29].

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was assessed for genotype distributions using a goodness-of-fit χ^2 test. Statistical analyses were performed using Sigma Stat Software (SYSTAT Software Inc., USA). Associations between genotypes and COVID-19 severity were evaluated using χ^2 test with Yates' correction under a dominant and recessive genetic model. Odds ratio (ORs) and 95% confidence intervals (CIs) were calculated from 2x2 contingency tables. A P-value ≤ 0.05 was considered statistically significant.

3. Results

Genotype distributions of the ACE I/D polymorphisms (rs4646994) were consistent with HWE in the overall study population (χ^2 test=3.05983, P=0.21655) with a statistical power of 90.59%. Demographic analysis revealed a higher proportion of males in the hospitalized (severe) group compared to the non-hospitalized group, whereas the proportion of females was similar between groups.

Regarding the ACE genotype, I/D heterozygous genotype was the most frequent in the total population (104/235). In the hospitalized group, the I/D genotype predominated, followed by the I/I genotype, whereas in the non-hospitalized group, the D/D genotype was the most frequent, followed by I/D (Table 1). A significant difference in genotype distribution between hospitalized and non-hospitalized subjects was observed (χ^2 = 11.65, p = 0.003). Under a dominant genetic model, individuals carrying at least one I allele (ID + II) showed a significantly increased risk of hospitalization compared to those with the DD genotype (OR = 2.78, 95% CI: 1.53-5.06, p = 0.001). In contrast, no significant association was observed under the recessive model (ID + DD vs II).

Sex-stratified analysis revealed that the association between ACE genotypes and disease severity was driven primarily by male patients. Among males, a significant difference in genotype distribution between hospitalized and non-hospitalized individuals was observed (χ^2 = 10.91, p = 0.004). Moreover, under dominant model (ID + II vs DD), male carriers of the I allele exhibited a

markedly increased risk pf hospitalization (OR = 5.79, 95% CI: 2.36-14.24, p = 9.6 x 10-4). No significant associations were detected among female participants under any genetic model (Table 1). In the hospitalized group, males represented 63.87% of cases, whereas females accounted for 36.12%.

For the TNF-α -308 G/A polymorphisms (rs1800629), genotype distribution were consistent with HWE in the hospitalized group (χ2 = 0.22353, P = 0.89425). The G/G genotype was the most frequent in both hospitalized or non-hospitalized groups, while the AA genotype was not observed in the study population. No significant differences in genotype frequencies or associations with COVID-19 severity were identified for this polymorphism (Table 2).

Table 1. Genotype frequencies for ACE-rs4646994 polymorphisms in COVID-19 hospitalized and non-hospitalized patients.

Genotype	Polymorphism for ACE in Hospitalized group No. (%)	Polymorphism for ACE in Non-hospitalized group No. (%)	χ ²	OR	95% CI	p-value
DD	30 (19.35)	32 (39.50)	11.65	0.721	0.392-1.326	0.003*
ID	76 (49.03)	28 (34.56)				
II	49 (31.61)	20 (24.69)				
ID+DD	76 (49.03) + 30 (19.35)	28 (34.56) + 32 (39.50)	0.817	0.721	0.392-1.326	0.366
ID+ II	76 (49.03) + 49 (31.61)	28 (34.56) + 20 (24.69)	10.541	2.778	1.526 – 5.057	0.001*

Genotype by gender	Polymorphism for ACE in Hospitalized group No. (%)	Polymorphism for ACE in Non-hospitalized group No. (%)	χ ²	OR	95% CI	p-value
Male	DD	19 (19.19)	10.906	0.721	0.221-1.436	0.004*
	ID	48 (48.48)				
	II	32 (32.32)				
	ID + DD	48 (48.48) + 19 (19.19)	0.983	0.721	0.221-1.436	0.322
	ID + II	48 (48.48) + 32 (32.32)	14.478	5.792	2.355-14.242	9.6e-4*
Female	DD	13 (23.21)	1.855	1.045	0.438-2.497	0.396
	ID	28 (50)				
	II	15 (26.78)				
	ID + DD	28 (50) + 13 (23.21)	0.0151	1.045	0.438-2.497	0.902
	ID + II	28 (50) + 15 (26.78)	0.994	1.707	0.719-4.056	0.319

Data are presented as the number of patients and percentages. CI: confidence interval, OR: odds ratio, p-values *, Power 90.59%.

Table 2. Genotype frequencies of TNF-α -308G/A rs1800629 polymorphisms in COVID-19 hospitalized and non-hospitalized patients.

Genotype	Polymorphism for TNF-α in Hospitalized group No. (%)	Polymorphism for TNF-α in non-hospitalized group No. (%)	χ ²	OR	95% CI	p-value
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GG	142 (92.30)	76 (96.20)				
AG	12 (7.69)	3 (3.79)	0.800	0.467	0.128-1.706	0.371

Data are presented as the number of patients and percentages. CI: confidence interval, OR: odds ratio, p-values*.

4. Discussion

COVID-19 has caused substantial morbidity an mortality worldwide. According to the World Health Organization, by November 6, 2022, more than 629 million cases and 6.5 million deaths had been reported globally, with over 372000 new cases registered in the Americas alone [1]. Although several clinical risk factors for severe COVID-19 have been well established; increasing evidence supports a contribution of host genetic factors to disease susceptibility and severity.

Genes involved in viral entry and inflammatory regulation, such as those of the renin-angiotensin system, have been proposed as key modulators of COVID-19 outcomes. Polymorphisms in the ACE2 gene, are of particular interest due to their influence on angiotensin II levels and inflammatory responses, which are critical in COVID-19 pathophysiology [23]. In the present study, we observed a significant association between the ACE I/D polymorphism and COVID-19 severity in a Mexican population, with carriers of the I allele (ID + II genotypes) showing an increased risk of hospitalization. Previous studies have reported heterogeneous results regarding the association between the ACE I/D polymorphisms and coronavirus-related disease. Chan et al. evaluated the ACE I/D polymorphism in relation to SARS-CoV susceptibility and acute respiratory distress syndrome (ARDS) and found no significant association [30]. Conversely, Itoyama et al. reported that this polymorphism was associated with hypoxemic in Vietnamese patients with SARS [31]. More recently, studies evaluating COVID-19 severity have also produced inconsistent findings, with some reporting no association [32]. Others including meta-analysis in European and Asian populations, suggested that the DD genotype is associated with increased disease severity compared to ID and II genotypes [16, 32-34]. In contrast to these reports, our results indicate a predominance of the I/D genotype among hospitalized patients whereas the DD genotype was more frequent in non-hospitalized individuals. Delanghe, Speeckaert, and De Buyzere proposed that populations severely affected by COVID-19, particularly in Asia, exhibit lower frequencies of the D allele [35]. This observation is consistent with our findings, as the hospitalized group in our study showed a lower frequency of the allele D, whereas the non-hospitalized group presented a higher frequency of this allele. These discrepancies across studies may reflect geographic and ethnic differences in allele distribution, as well as population specific genetic backgrounds, as previously suggested by by Pabalan et al. and some other studies [21, 33, 35, 36].

In Mexican populations, I/D genotype has been reported as the most frequent ACE polymorphism among healthy individuals [37]. In our study, this genotype was also predominant among hospitalized patients but not among non-hospitalied individuals, suggesting a potential role of the I allele in disease seveity rather than susceptibility. However, this finding should be interpreted cautiously, considering the complex interaction between genetic, environmental, and clinical factors in COVID-19 progression. Sex-based differences were also observed in our cohort, with males beng more frequently hospitalized than females, in agreement with previous reports [38, 39]. Furthermore, the association between the ACE I/D polymorphism and disease severity remained significant in males after sex stratification, whereas no significant associations were observed among females. These results are consistent with previous studies reporting sex-specific genetic effects and suggest that hormonal, immunological or behavioral factors may modulate the impact of ACE polymorphisms on COVID-19 outcomes. Although ACE I/D polymorphisms have been extensively studied in relation to hypertension in Mexican populations, no consistent associations have been stablished, underscoring the complexity of ACE-related phenotypes [27, 40].

The inflammatory response plays a central role in COVID-19 severity, particularly through the development of a cytokine storm in critically ill patients [24]. Elevated levels of pro-inflammatory

cytokines including TNF- α , have been associated with poor prognosis [41]. In the present study, the TNF- α -308G/A (rs1800629) polymorphism showed genotype frequencies consistent with those previously reported in Mexican populations [42]. The GG genotype was predominant in both hospitalized and non-hospitalized groups, and the AA genotype was not detected. Non-significant association between TNF- α -308G/A polymorphism and COVID-19 severity was observed. Although a slightly higher frequency of the AG genotypes was found among hospitalized patients, this difference did not reach statistical significance. Previous studies have suggested that carriers of the A allele may have a worse prognosis due to increased TNF- α expression [43]. However, the low frequency of the A allele and the absence of the AA genotype in our cohort may have limited the ability to detect such an association. Similar findings have been reported in studies comparing severe and asymptomatic or mildly symptomatic COVID-19 patients [44]. Rokni et al. reported an association between the TNF- α A allele and disease severity, particularly in individuals with the AA genotype, while other cytokine-related polymorphisms showed no significant associations [45].

Several limitations of this study should be acknowledged. The relatively small sample size of the non-hospitalized group may have reduced the statistical power to detect modest genetic effects, particularly for low-frequency alleles such as TNF- α -308 A. Additionally, healthy, SARS-CoV-2-negative controls were not included, which limits the assessment of genetic susceptibility versus disease severity. Another important limitation is the lack of multivariate analysis adjusting for potential confounders such as age, sex, and comorbidities, which may influence both genotype distribution and clinical outcomes. Future studies with larger sample sizes, inclusion of healthy controls, and multivariable models are warranted to further clarify the role of ACE and TNF- α polymorphisms in COVID-19 severity. Nonetheless, our findings contribute to the understanding of host genetic factors involved in COVID-19 in the Mexican Population and highlight the importance of considering population-specific genetic backgrounds.

5. Conclusions

Our findings indicate that the ACE I/D polymorphism is associated with COVID-19 severity in a Mexican population, with a stronger association observed in male patients. In contrast, no significant association was identified for the TNF- α -308 G/A polymorphism. These results support the relevance of host genetic factors in modulating disease severity and highlight the importance of considering sex-specific effects and population genetic background in COVID-19 research. Further studies with larger sample sizes, inclusion of healthy controls, and multivariable analyses are warranted to confirm these associations and to clarify their potential clinical implications.

Author Contributions: MAM processed the samples and obtained data. MAM and MSS analyzed data, performed the statistical analysis, and wrote the manuscript. MSs, LGF, and ORT collected and processed the samples and obtained data. AMC guided the work, organized and designed the study, critically revised the manuscript's content, and wrote the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate: The General Hospital Saltillo Investigation Ethic Committee approved the study according to the NOM-012-SSA3-2012, which covers the execution of health research protocols in humans or samples of human origin, # 17/2023.

Data Availability Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: Declare conflicts of interest or state "The authors declare no conflicts of interest." Authors must identify and declare any personal circumstances or interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results. Any role of the funders in the design

of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript; or in the decision to publish the results must be declared in this section. If there is no role, please state “The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results”.

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