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.

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Letter to the Editor

An observed association between angiotensin-converting enzyme 2 polymorphisms and COVID-19 severity in China

Dear Editor,

We read with great interest several works on the angiotensin-converting enzyme (ACE) polymorphism findings for COVID-19 published in the Journal of Infection.[1,2] The association between the prevalence of the deletion/deletion (DD) and insertion/insertion (II) ACE genotypes and COVID-19 mortality was evaluated across 25 countries, representing a diverse cross-section of various geographical regions of the world. The results revealed that a high frequency of the II genotype of ACE was significantly associated with low COVID-19 mortality rates, but the DD genotype did not exhibit a noteworthy correlation.[2] Additionally, replication analysis did not reveal a significant association between these genotypes and the prevalence and mortality of COVID-19, which was investigated in the European population.[1] These conflicting results have attracted our attention, and the association between ACE polymorphisms and COVID-19 requires further clarification.

In the renin-angiotensin system (RAS), a counterregulatory relationship between ACE and ACE2 that can counteract the impact of ACE has been revealed.[3] Membrane-bound ACE2 receptors allow SARS-CoV-2 to enter alveolar epithelial cells, leading to endothelial dysfunction and the activation of a severe maladaptive immune response. This process is a hallmark of acute respiratory distress syndrome (ARDS) and a common occurrence in severe COVID-19 patients.[3] Since the outbreak of the COVID-19 pandemic, the function of ACE and ACE2 gene polymorphisms in disease severity has been brought into focus again. Unlike the findings for ACE polymorphisms, many single nucleotide polymorphisms (SNPs) in the ACE2 receptor gene, such as rs2285666, have been reported to be associated with the infection rate as well as the case-fatality rate of COVID-19 in the Indian population.[4] Moreover, through using several beneficial bioinformatics tools, many ACE2 SNPs have also been identified to impact susceptibility to COVID-19 in different populations.[5] Extensive studies have also shown that patients with underlying cardiovascular disease and/or cardiac risk factors are more susceptible to SARS-CoV-2 infection, suggesting a strong link between them.[6] The ACE II genotype was associated with an approximately 2-fold increase in the risk of diabetes for cardiovascular disease patients, and ACE2 SNPs associated with cardiovascular disease risk have also been gradually discovered[7] In addition, the ACE2 SNP rs879922 was associated with diabetes-related cardiovascular complications and might be a common genetic mutation. Thus, it may be an ideal marker for genetic susceptibility to diseases in Uyghurs.[8] A correlation was also found between the ACE2 SNP rs233575 and blood pressure, and ACE2 risk alleles were associated with more severe COVID-19 outcomes in obese, smoking males.[9] Specifically, two missense variants (K26R and S331F) were shown to reduce the binding affinity of the viral spike (S) protein to the ACE2 receptor[10], which implies that this ACE2 polymorphism may affect the prevalence and mortality of COVID-19.

In our study, five intronic ACE2 polymorphisms (rs4646142, rs2048683, rs4240157, rs6632677, and rs2074192) were found to be associated with cardiovascular disease based on our primary literature search from PubMed. Then, these polymorphisms were chosen to further analyze their effects on the severity of COVID-19. A total of 196 whole blood samples were collected from COVID-19 patients who were diagnosed with COVID-19 by laboratory testing at Shanghai Public Health Clinical Center (Shanghai, China). The baseline clinical characteristics were as follows: 98 males, 98 females, 2 mild-type cases, 184 common-type cases, 7 severe-type cases, and 3 critical-type cases. Among the 196 patients with COVID-19 enrolled in our study, the average age of COVID onset was 49.36 ± 14.78 years, and the average ages were 18.50 ± 3.53, 49.01 ± 14.36, 60.14 ± 15.19 and 66.33 ± 7.37 years for the mild, common, severe and critical groups, respectively. There were 42 common, 3 severe and 1 critical patients who suffered from hypertension. There were 18 common, 2 severe and 1 critical patients who suffered from diabetes. There were 7 common and 1 severe patients who suffered from heart disease.

Considering the effect of ACE2 on the pathogenesis of COVID-19, ACE2 SNPs have attracted our attention. The ACE2 rs2074192, rs6632677, rs4646142, rs2048683, and rs4240157 polymorphisms were first investigated in COVID-19 patients using TaqMan® SNP Genotyping Assays in a LightCycler® 480 II system. The distribution of each genotype and allele frequency for the ACE2 SNPs in the COVID-19 patients according to the severity of the disease is listed in Table 1. We demonstrated that there was a statistically significant correlation between the severity and the distribution of genotypes ($p = 0.027$) and allele frequencies ($p = 0.003$) for ACE2 SNP rs6632677. However, the distribution of the genotypes and allele frequencies of the ACE2 rs2074192, rs4646142, rs2048683 and rs4240157 gene polymorphisms were not significantly different ($p > 0.05$). Our findings also verified that ACE2 SNP rs6632677 correlated with COVID-19 severity and may be a valuable genetic marker for determining the degree of severity in COVID-19 patients. These findings imply a possible relationship between ACE2 SNPs and the severity of COVID-19, and this relationship needs further research in large-scale studies.

Ethical approval

The study was performed under approval by the Ethics Committee of Shanghai Public Health Clinical Center.

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Table 1
Genotype/allele distribution of ACE2 SNPs in COVID-19 patients according to the severity of the disease.

SNP	Genotype/Allele	Severity				χ^2	*P value*
		Mild (%)(n = 2)	Common (%)(n = 184)	Severe (%)(n = 7)	Critical (%)(n = 3)		
rs4646142	GG	0 (0)	60 (32.61)	3 (42.86)	1 (33.33)	1.879	0.9305
	GC	1 (50)	48 (26.09)	1 (14.29)	1 (33.33)		
	CC	1 (50)	60 (32.61)	3 (42.86)	1 (33.33)		
	G	1 (25)	168 (50)	7 (50)	3 (50)	0.9889	0.8039
	C	3 (75)	168 (50)	7 (50)	3 (50)		
rs20248683	TT	0 (0)	1 (0.54)	0 (0)	0 (0)	1.753	0.941
	GT	0 (0)	22 (11.96)	0 (0)	0 (0)		
	GG	2 (100)	156 (84.78)	7 (100)	3 (100)		
	T	0 (0)	24 (6.7)	0 (0)	0 (0)	1.717	0.6332
	G	4 (100)	334 (93.3)	14 (100)	6 (100)		
rs4240157	CC	0 (0)	6 (3.26)	1 (14.29)	0 (0)	2.778	0.8362
	CT	0 (0)	4 (2.17)	0 (0)	0 (0)		
	TT	2 (100)	172 (93.48)	6 (85.71)	3 (100)		
	C	0 (0)	16 (4.4)	2 (14.29)	0 (0)	3.480	0.3233
	T	4 (100)	348 (95.6)	12 (85.71)	6 (100)		
rs6632677	GG	1 (50)	160 (86.96)	5 (71.43)	3 (100)	14.23	0.0272*
	GC	0 (0)	15 (8.15)	0 (0)	0 (0)		
	CC	1 (50)	9 (4.89)	2 (28.57)	0 (0)		
	G	2 (50)	335 (91.03)	10 (71.43)	6 (100)	13.64	0.0034**
	C	2 (50)	33 (8.97)	4 (28.57)	0 (0)		
rs2074192	CC	1 (50)	78 (42.39)	4 (57.14)	1 (33.33)	1.921	0.9268
	CT	1 (50)	45 (24.46)	1 (14.29)	1 (33.33)		
	TT	0 (0)	56 (30.43)	2 (28.57)	1 (33.33)		
	C	3 (75)	201 (56.15)	9 (64.29)	3 (50)	1.024	0.7955
	T	1 (25)	157 (43.85)	5 (35.71)	3 (50)		

P value is for Chi-square test.

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Declaration of Competing Interest

No conflicts of interest are declared by the authors.

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