Letter to the Editor

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ACE polymorphism is a determinant for COVID-19 mortality in the post-vaccination era

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To the Editor,

The COVID-19 pandemic has been responsible for over 4,500,000 lethal cases worldwide by September 2021. Despite a huge vaccination campaign by all European countries in 2021, COVID-19 still causes a considerable human toll. As COVID-19 prevalence and mortality partially depends on genetic factors [1, 2], we have studied the potential effect of several genetic polymorphisms on COVID-19 mortality in the post-vaccination period. Incidence and case mortality data from 26 European countries were compared with the proportion of fully vaccinated people in each country, and the phenotype distribution of several genetic polymorphisms: ABO blood group, galactoside 2-alpha-L-fucosyltransferase 2 (FUT2), deletion/insertion (D/I) of angiotensin-converting enzyme 1 (ACE1), complement C3, haptoglobin, vitamin D binding protein (DBP), the cystic fibrosis mutation, and the homeostatic iron regulator protein (HFE). Data from Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Luxemburg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK, as communicated by the European Centre for Disease Prevention and Control were included in the study [3].

Table 1 summarizes the final model of a multiple regression model (after stepwise elimination of the non-significant genetic polymorphisms). In this model, the relative mortality (the ratio of death rate and case rate in a given country) was compared to the vaccine uptake in adults, week 34, 2021 for each country. As expected, vaccination protects against COVID-19 mortality (p=0.0026). Furthermore, also the ACE1 D/I polymorphism independently contributes (p=0.0076) to COVID-19 mortality (see Figure 1).

The *ACE1* gene is characterized by a genetic D/I of an Alu repeat in intron 16 and this polymorphism (rs1799752) shows an important geographical variation [4]. The ACE1 DD genotype is associated with lower expression of ACE2 in human tissues [4]. As SARS-CoV-2 host cell attachment is predominantly facilitated by the ACE2 receptor [5], ACE2 counteracts the effects of its homolog ACE1 [6]. An ACE1/ACE2 imbalance plays an important role in SARS-CoV-2 infectivity and COVID-19 progression [6]. Whereas the ACE1 D allele seems to be protective in the unvaccinated population [1, 2], on the other hand, the ACE1 D allele has been associated with an increased risk of hypertension, pre-eclampsia, heart failure, cerebral infarct, diabetic nephropathy, encephalopathy, asthma, severe hypoglycaemia in diabetes, gastric cancer, and poor prognosis following kidney transplant. Many of these

Table 1: Multivariate model for predicting relative COVID-19 mortality for 26 European countries (death rate/case rate) (r^2=0.535, p=0.0002). Data from September 3, 2021.

Parameter	Coefficient	Standard error	t	p-Value	VIF
Constant	−0.1211				
Vaccination coverage (% fully vaccinated adults)	−0.001614	0.000478	−3.385	0.0026	1.024
ACE1 D allele frequency	0.00495	0.00169	3.309	0.0076	1.024

ACE, angiotensin-converting enzyme 1; VIF, variance inflation factor.

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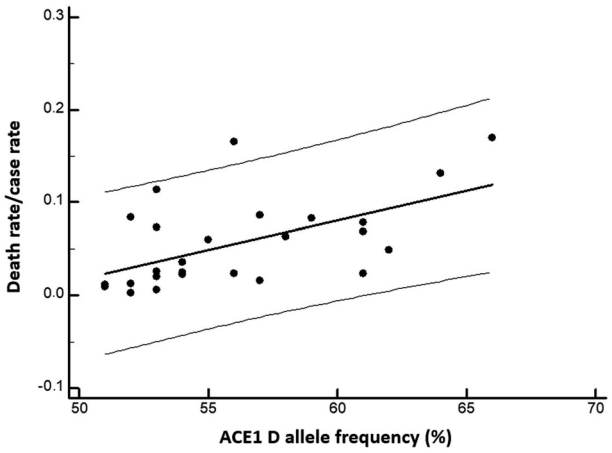

Figure 1: Relative mortality due to COVID-19 and ACE1 D allele frequency in 26 European countries.
Y (relative mortality due to COVID-19) = 0.00636 X (ACE1 D allele frequency, %) −0.300 (r^2=0.3122; p=0.01).

conditions have been associated with a poorer outcome following COVID-19 infection [8]. On the positive side, the ACE1 D allele confers greater upper-body strength in old age. The ACE1 I allele, meanwhile, offers improved endurance/athletic performance and aerobic capacity, although it does increase the risk of obstructive sleep apnea in hypertensives [7].

Next to the expected effect of the widespread vaccination campaign, in Europeans the ACE1 D allele appears to be a major confounding factor in COVID-19 mortality, which is able to partially explain the pronounced geographical differences in COVID-19 in the post-vaccination era.

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