ABO blood groups and COVID-19

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TO THE EDITOR - We read with interest the study by Zhao et al. [1], in which ABO blood groups were associated with COVID-19 in Chinese patients. Similarly, Ellinghaus et al. [2] recently described an effect of ABO blood group polymorphism on respiratory failure in COVID-19 in Spanish and Italian patients. As ABO blood group allele frequencies show an important geographical variation [3] and as ABO polymorphism cosegregates with other genetic markers [4], we compared ABO allele frequencies and COVID-19 mortality from 54 countries of the Northern hemisphere: Albania, Algeria, Austria, Bangladesh, Belgium, Belarus, Bosnia, Bulgaria, China, Croatia, Cyprus, Czech Republic, Denmark, Djibuti, Egypt, Ethiopia, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Indonesia, Iran, Israel, Italy, Japan, Jordan, Latvia, Lithuania, Luxemburg, Malta, Moldova, Morocco, Netherlands, Norway, Oman, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tunesia, Turkey, and the United Kingdom [4] . COVID-19 mortality data reported on April 30, 2020 by Johns Hopkins were analyzed [5].

As the 'decoration' of human cells with ABO blood group antigens results from both the genetic variation of the *ABO* gene (located on chromosome 9q34.2), as well of the secretor gene [defined by the *FUT2* gene (19q13.33)], the geographical distribution of the *FUT2* gene was studied in parallel [3]. The time interval since the start of the infection in each country was recorded to synchronize the data.

A significant correlation between ABO allele frequencies and COVID-19 mortality was found, in which the B allele frequencies correlated with mortality (Table 1). The B allele frequency, as well as the complement C3 (C3), and angiotensin converting enzyme 1 (ACE1) polymorphisms were significant determinants for predicting COVID-19 mortality (r^2 = 0.711). The *FUT2* gene did not show a correlation with COVID-19 prevalence/mortality.

Although an association was found between the A and B allele frequencies, and COVID-19 mortality using univariate analysis, the A allele frequency lost its significance when other polymorphisms (C3, ACE1) were integrated into the model. The ABO polymorphism shows a marked Eurasian East-West gradient (the A allele is associated with the sixth principal component), [3] which comigrates with causal genetic factors involved in COVID-19. SARS-CoV spike proteins interact with blood group antibodies [6]. In a multivariate analysis model describing the pandemic in a large geographical area, the role of the A allele in COVID-19 was secondary, whereas the importance of the B allele in COVID-19 was demonstrated.

Potential conflicts of interest. None. *The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.*

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Table 1: Multivariate model for predicting COVID-19 mortality (n/10^6 inhabitants) (r^2 = 0.711, p <0.0001). Data from April 30, 2020.

Parameter	Coefficient	Standard error	t	p-value	VIF
constant	13.204				
ABO blood group (A allele frequency)	-0.017	0.0277	-0.629	n.s.	2.159
ABO blood group (B allele frequency)	0.097	0.017	-5.645	<0.0001	1.277
C3 S allele frequency	-0.091	0.024	-3.753	0.0006	3.729
ACE D allele frequency	-0.022	0.009	-2.569	0.0141	1.686
Start of pandemic (days since January 1, 2020)	-0.013	0.005	-2.547	0.0148	1.780

Abbreviations: ACE, angiotensin-converting enzyme; C3 (S), complement component 3 (slow); n.s., not significant; VIF, variance inflation factor