Comparison of COVID-19 outcomes with alpha-1-antitrypsin deficiency prevalence: A cross-sectional study.

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Abstract

Background: We hypothesized that the geographic distributions of COVID-19 prevalence and risky alpha-1-antitrypsin allele prevalence are similar. We aimed to investigate whether there is a relationship between the geographical density of the COVID-19 pandemic and the distributions of risky alpha-1-antitrypsin alleles. Methods: This research is a cross-sectional study. Alpha-1-antitrypsin PI*SZ and PI*ZZ genotypes frequencies of European and American countries were compared with the case and death data related to the COVID-19 pandemic as of March 30, 2021. The relationship between the data was evaluated using Linear regression analysis. Results: According to the linear regression analysis results, a significant relationship was found between the number of COVID-19 cases in both European and American countries and the sum of PI*SZ and PI*ZZ genotypes. Similarly, according to the linear regression analysis results, a significant relationship was found between the COVID-19 death numbers in both European and American countries and the sum of PI*SZ and PI*ZZ genotypes. Conclusions: The findings showed that the prevalence distribution of the risky alleles of the gene defect that causes alpha-1-antitrypsin insufficiency is related to the prevalence of COVID-19 pandemic data.

1. INTRODUCTION

Alpha-1-antitrypsin (A1AT) belongs to the serpine protease inhibitor (serpin) family, as are alpha-1-antichymotrypsin, C1 inhibitor, antithrombin, and neuroserpine. It is known as alpha-1-antiproteinase and is also encoded as a proteinase inhibitor (PI).[1]A1AT is synthesized by hepatocytes, macrophages, intestinal epithelial cells, and bronchial epithelial cells.[2,3] With a plasma half-life of five days, A1AT is found in all body fluids and most tissues. A1AT is an acute-phase protein and one of the potent regulators of neutrophil activation, acting through protease inhibition and other mechanisms.[4] On the other hand, A1AT is the strongest inhibitor of bacterial serine proteases, proteinase 3, and neutrophil elastase.[4,5]

The A1AT gene consists of two alleles. Most of the genotype distribution in the human population are combinations of the M, S, and Z alleles. Furthermore, the PI*MM genotype is considered normal, which is encountered in 85-95% of the world population and can synthesize 100% normal A1AT.[6] On the other hand, the genotype distributions of PI*MS, PI*SS, PI*MZ, PI*SZ, and PI*ZZ alleles are 5-15% worldwide. These alleles can achieve 80%, 60%, 55%, 40%, and 15% normal A1AT synthesis, respectively.[7]

Most of the mutations in the A1AT gene result in mutant protein synthesis that lacks function and damages the cell where it accumulates.[8] The PI*ZZ genotype carries a high risk of diseases associated with A1AT insufficiency, while the PI*SZ, PI*SS, and PI*MZ genotypes are only potentially risky.[9,10]Especially the PI*SZ allele causes pulmonary emphysema in smokers.[7]

The SARS-CoV-2 virus (COVID-19) was identified as a result of research conducted on a group of patients with acute respiratory symptoms in the form of fever, cough, and shortness of breath in Wuhan Province,

China, in late 2019.[11] Approximately 81% of symptomatic patients infected with COVID-19 show mild, 14% severe, and 5% critical disease course.[12]

A study covering 97 countries with a total sample of 5.264 million projected that there are 190 million carriers of a risky allele in the A1AT.[10] Of these alleles 142 million (74.8%) are PI*MS, 42 million (22.3%) are PI*MZ, 4 million (2.1%) are PI*SS, 1.269 million (0.7%) are PI*SZ, 181,000 (0.1%) are PI*ZZ genotype.[10]

We hypothesized that the geographic distributions of COVID-19 prevalence and risky A1AT allele prevalence are similar. Therefore, we aimed to investigate whether there is a relationship between the geographical density of the COVID-19 pandemic and the distributions of risky A1AT alleles.

2. MATARIALS AND METHODS

2.1. Study Design

This research is a cross-sectional study.

2.2. Variables

Data[6,7] showing the sum of A1AT PI*SZ and PI*ZZ genotypes numbers of countries in Europe and America were compared with the case and mortality numbers related to the COVID-19 pandemic as published by Worldometer[13] on March 30, 2021 (Table 1, Table 2).

Since the A1AT PI*SZ and PI*ZZ data of countries other than Europe and America are insufficient and the numbers of COVID-19 pandemic cases and deaths in the Worldometer database were not considered reliable for each country, only the data of these two regions have been analyzed. In addition, Iceland from the European continent was excluded from the study due to the lack of data, and Russia was excluded because of the low reliability of the data as well as its geographical location in the Asian continent.

2.3 Statistical analyzes

All statistical analyzes were performed by using IBM SPSS software (V25). The distribution of the data was assessed by the Kolmogorov-Smirnov test. The relationship between the data was evaluated using Linear regression analysis.. The threshold for statistical significance was taken as $P< 0.05$.

2.4. Ethical approval

No ethical approval was required for this study. The study data were obtained from public sources and related literature. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. RESULTS

According to the linear regression analysis results, a significant relationship was found between the number of COVID-19 cases in both European [R2 = 0.721; F (1, 19) = 49.19; P= 0.001] and American [R2 = 0.972; F (1, 19) = 661.71; p= 0.001] countries and the sum of PI*SZ and PI*ZZ genotypes (Table 3).

Similarly, according to the linear regression analysis results, a significant relationship was found between the COVID-19 death numbers in both European [R2 = 0.602; F (1, 19) = 28.72; P= 0.001] and American [R2 = 0.921; F (1, 19) = 221.65; P= 0.001] countries and the sum of PI*SZ and PI*ZZ genotypes (Table 4).

4. DISCUSSION

Produced in the liver, A1AT has a protective function against proteolytic damage by inhibiting neutrophil elastase activity in the lungs. It provides approximately 90% of the protection against elastolytic activity caused by elastase released from neutrophils in the lower respiratory tract.[5,14,15]

Very few people infected with the SARS-CoV-2 virus develop respiratory failure that requires mechanical ventilation. This clinical situation associated with high mortality shows a wide geographic variation.[16] The

hypothesis that there may be a relationship between severe disease and A1AT distribution is supported in our study. As a matter of fact, a highly significant correlation has been found between the numbers of COVID-19 cases and deaths in European countries and the numbers of individuals with the A1AT PI*SZ and PI*ZZ genotypes.

In the European continent, the prevalence of the A1AT PI*SZ genotype is highest in the southern (1: 483) and western (1: 581) regions and lowest in the eastern part (1: 11818).[7] When the distribution of COVID-19 pandemics is investigated, it seems that Southern and Western European countries are more affected by the intensity of infection.[13] Additionally, mortality rates are high in this population.[17]

In a screening study conducted in Italy, 70 of 859 samples were found to have A1AT deficiency, and 80% had the PI*ZZ genotype.[18] Interestingly, more than 90% of the patients with this insufficiency are in the northern regions. It was also claimed that the proportion of both PI*S and PI*Z alleles of the A1AT gene was higher in the Northern Italy region.[19]Similarly, the current database of the COVID-19 pandemic shows that infection rates are higher in the Northern Italy region.[20] In addition, an Italy-focused study suggested that the distribution of the COVID-19 pandemic and A1AT deficiency coincided geographically, and this could not be explained by a random relationship.[21]

In a study conducted in the USA, it was claimed that the highest risk for A1AT deficiency was in whites, that is, those of European descent, followed by Mexicans and blacks, and the lowest risk was among those of Asian descent.[22] While the prevalence of the A1AT PI*ZZ allele in the world is around 0.3%, it is estimated to be about 1% in the European continent.[23] In addition, almost half of the total 1.269 thousand PI*SZ genotypes calculated in the world are in Europe (74% in Spain, Portugal, France, and England), one fifth in North and Central America (60% in the USA), and one-sixth in South America (55% in Brazil).[10] In countries such as the USA and Brazil, especially in Southern and Western Europe, both the case and death rates of the COVID-19 pandemics appear to be significantly higher.[13] In our study, in line with this geographical distribution, a highly significant correlation was found between the numbers of COVID-19 cases and deaths belonging to the American continent and the number of individuals with the A1AT PI*SZ and PI*ZZ genotypes. In a similar study conducted in the first months of the pandemic, it was suggested that there may be a relationship between the geographic distribution of A1AT deficiency and covid deaths.[24]

Furthermore, the proportion of individuals with the PI*MM genotype that synthesize the normal A1AT protein varies between 85% and 95%, depending on the countries.[7] Among alleles that cause A1AT insufficiency, the proportion of individuals with the PI*MS and PI*MZ genotypes that are considered low risk is 96%, and the rate of individuals with the PI*SS, PI*SZ, and PI*ZZ genotypes that are regarded as high risk is around 4%.[10] Due to the fact that 81% of symptomatic patients infected with COVID-19 have a mild, 14% have severe, and 5% have a critical illness, it is thought that the severity of the disease goes hand in hand with the A1AT allele rates.[12]

5. CONCLUSIONS

We conclude that the prevalence distribution of the risky alleles of the gene defect that causes A1AT insufficiency, which is one of the most important protective factors of lung tissue, is related to the prevalence of COVID-19 pandemic data. More detailed studies are needed on the relationship between A1AT and COVID-19 in order to confirm this argument, which we think can contribute significantly to combating the COVID-19 pandemic.

Limitations: Restriction of the source articles concerning A1AT data should be considered as our limitations.

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Table 1: Distribution of COVID-19 cases and deaths and the number of individuals with alpha-1-antitrypsin PI*SZ and PI*ZZ genotypes in European countries.

Locations	Countries	Worldometer COVID-19 data Cases	Worldometer COVID-19 data Death	A1AT data PI*SZ	A1AT data PI*ZZ
Northern Europe	Denmark	229902	2417	8435	4090
	Estonia	105416	896	790	752
	Finland	76845	826	2098	1929
	Latvia	101733	1893	5546	4005
	Lithuania	215216	3566	1406	717
	Norway	94622	661	4808	1798
	Sweden	796445	13430	4732	2262
Western Europe	Belgium	872936	22921	20718	3193
	France	4554683	94956	161680	17191
	Netherlands	1264983	16509	27586	5353
	Ireland	235444	4681	11230	2265
	UK	4341736	126670	73973	13144
Central Europe	Austria	542542	9308	5186	1529
	Germany	2800917	76664	60396	20611
	Poland	2288826	52392	14381	6791
	Switzerland	598713	10310	6581	972
Southern Europe	Italy	3561012	108879	64137	10652
	Portugal	821104	16845	52836	4944
	Spain	3275819	75305	174882	14522
Eastern Europe	Macedonia	127240	3716	446	142
	Serbia	595489	5270	1202	1159

Table 2: Distribution of COVID-19 cases and deaths and the number of individuals with alpha-1-antitrypsin PI*SZ and PI*ZZ genotypes in American countries.

Locations	Countries	Worldometer COVID-19 data Cases	Worldometer COVID-19 data Death	A1AT data PI*SZ	A1AT data PI*ZZ
North America	Canada	971718	22900	38997	7181
	USA	31038550	563259	254641	62820
	Mexico	2227842	201826	49590	3921
South America	Argentina	2322611	55611	18133	1669
	Bolivia	270347	12211	3517	305
	Brazil	12577354	314268	105486	6162
	Chile	984484	23070	8235	708
	Colombia	2389779	63079	23327	1995
	Ecuador	325124	26222	6786	579

	Paraguay	210425	4113	3584	305
	Peru	1533121	51635	11955	1046
	Uruguay	99584	928	1320	121
	Venezuela	157943	4040	25103	1897
Central America	Costa Rica	215178	2931	3384	286
	Cuba	73204	417	6496	548
	Dominican	252384	3317	4971	425
	El Salvador	64431	2006	3256	274
	Guatemala	193556	6809	5681	488
	Honduras	187975	4584	4168	357
	Nicaragua	6629	177	2809	239
	Panama	470175	9086	1541	133

Table 3: Regression analysis showing the relationship between PI*SZ and PI*ZZ allele sum and COVID-19 case numbers.

Coefficients[a]		
Grups	Variable	B
Europe	(Constant)	412500.61
	Pi*SZ&ZZ	22.94
R = 0.849 R^2 = 0.721 F (1,19) = 49.19 P = 0.001	R = 0.849 R^2 = 0.721 F (1,19) = 49.19 P = 0.001	R = 0.849 R^2
America	(Constant)	-475168.87
	Pi*SZ&ZZ	98.67
R = 0.986 R^2 = 0.972 F (1, 19) = 661.71 P = 0.001	R = 0.986 R^2 = 0.972 F (1, 19) = 661.71 P = 0.001	R = 0.986 R^2

[a]Dependent Variable: Case; SE: Standard Error; B: Unstandardized Coefficients; Beta: Standardized Coefficients; R^2 = R square; Linear regression analysis is significant at the P< 0.05 level (2-tailed).

Table 4: Regression analysis showing the relationship between PI*SZ and PI*ZZ allele sum and COVID-19 death numbers.

Coefficients[a]		
Grups	Variable	B
Europe	(Constant)	8747.34
	Pi*SZ&ZZ	0.566
R = 0.776 R^2 = 0.602 F (1,19) = 28.72 P = 0.001	R = 0.776 R^2 = 0.602 F (1,19) = 28.72 P = 0.001	R = 0.776 R^2
America	(Constant)	5013.74
	Pi*SZ&ZZ	1.87
R = 0.960 R^2 = 0.921 F (1, 19) = 221.65 P = 0.001	R = 0.960 R^2 = 0.921 F (1, 19) = 221.65 P = 0.001	R = 0.960 R^2

[a]Dependent Variable: Death; SE: Standard Error; B: Unstandardized Coefficients; Beta: Standardized Coefficients; R^2 = R square; Linear regression analysis is significant at the P< 0.05 level (2-tailed).