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Prevalence and mortality of COVID-19 are associated with the L55M functional polymorphism of Paraoxonase 1

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Abstract

Introduction: Accumulating evidence recommends that infectious diseases including coronavirus disease 2019 (COVID-19) are often associated with oxidative stress and inflammation. Paraoxonase 1 (*PON1*, OMIM: 168,820), a member of the paraoxonase gene family, has antioxidant properties. Enzyme activity of paraoxonase depends on a variety of influencing factors such as polymorphisms of *PON1*, ethnicity, gender, age, and a number of environmental variables. The *PON1* has two common functional polymorphisms, namely, Q192R (rs662) and L55M (rs854560). The R192 and M55 alleles are associated with increase and decrease in enzyme activity, respectively.

Objective: The present study was conducted to investigate the possible association of rs662 and rs854560 polymorphisms with morbidity and mortality of COVID-19.

Methods: Data for the prevalence, mortality, and amount of accomplished diagnostic test (per 10^6 people) on 25 November 2020 from 48 countries were included in the present study. The Human Development Index (HDI) was used as a potential confounding variable.

Results: The frequency of M55 was positively correlated with the prevalence (partial r = 0.487, df = 36, p = 0.002) and mortality of COVID-19 (partial r = 0.551, df = 36, $p < 0.001$), after adjustments for HDI and amount of the accomplished diagnostic test as possible confounders.

Conclusions: This means that countries with higher M55 frequency have higher prevalence and mortality of COVID-19.

Keywords

COVID-19, ecologic study, mortality, paraoxonase 1, polymorphism

Introduction

In late December 2019, patients having a mysterious pneumonia were discovered in Wuhan, China. Today, it is named coronavirus disease 2019 (COVID-19). COVID-19 has rapidly spread from China to other countries worldwide,[1] and until now (25 November 2020), more than 61 million confirmed cases with about 1.4 million deaths have been reported from all around the world.

A lot of studies have indicated that various genetic and environmental elements are involved in etiology and prognosis of infectious diseases.[2–8] Therefore, it is really important to find out the factors that play a role in COVID-19 spreading. It should be noted that at the population level, understanding the relationship between the population genetic backgrounds as well as environmental factors and epidemiologic parameters of the COVID-19 plays a strategic role in making the best decision to control and prevent the pandemic.

Paraoxonase 1 (*PON1*, OMIM: 168,820), a member of the paraoxonase gene family, has antioxidant properties. Enzyme activity of paraoxonase depends on a variety of influencing factors such as polymorphisms of *PON1*, ethnicity, gender, age, and a number of environmental variables. The *PON1* has two common functional polymorphisms, that is, Q192R (rs662) and L55M (rs854560).[9] It is well acknowledged that

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the R192 and M55 alleles are related with augmented and reduced enzyme activity, respectively.[10]

Infectious diseases are often associated with oxidative stress and inflammation.[11,12] Low-serum PON1 activity is observed in bacterial and viral infections.[13–16] In septic patients, serum paraoxonase activity is remarkably decreased.[14] Accumulating evidence commends that oxidative stress increases the risk of infection of the human coronavirus HCoV 229E[17] and the SARS-CoV-2.[18–20]

There are limited ecologic and genetic association studies on relations between common genetic variations and morbidity/mortality of COVID-19.[21–25] However, there is no study considering the correlation between *PON1* polymorphisms and COVID-19. The rs662 and rs854560 are common functional polymorphisms. On the other hand, COVID-19 is associated with oxidative stress and inflammation. These provide solid rationale to carry out the present study.

Methods

Data for the prevalence, mortality, and amount of accomplished diagnostic test (per 10^6 people) on 25 November 2020 were achieved from the website www.worldometers.info/coronavirus/countries. The M55 and R192 allelic frequencies in different countries were acquired from preceding reports (Table 1). The amount of COVID-19 diagnostic tests accomplished per one million of the population in each country was also used as an additional variable.

The Human Development Index (HDI) is a statistic compound index which reflects three very important dimensions of human development, including life expectancy at birth, education (including literacy rate, gross enrollment ratio at different levels, and net attendance ratio), and the gross national income (PPP) per capita. The HDI is the geometric mean of the above-mentioned normalized indices. The HDI is estimated for countries. Countries with higher life expectancy, income, and educational levels have higher HDI value. To measure the level of human development for a given country, as well as to compare with other countries, researchers frequently used the HDI values. The HDI values are calculated annually and reported by the United Nations Development Program's Human Development Report Office. The 2019 report is the latest one, which was used in the present study.

Data from 48 countries were used in the analysis. These countries are: Argentina, Australia, Austria, Benin, Brazil, Canada, Chile, People's Republic of China, Costa Rica, Cuba, Czech Republic, Denmark, Dominican, Egypt, Estonia, Ethiopia, Finland, France, Germany, Greece, Hungary, India, Iran, Ireland, Italy, Japan, Malaysia, Mexico, Morocco, The Netherlands, Peru, Poland, Portugal, Qatar, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Thailand, Tunisia, Turkey, United Kingdom, Ukraine, and United Sates of America.

Pearson correlation analysis and partial correlation analysis were used to examine the relationship between the selected epidemiological indices and the explanatory variables. Analyses were achieved using SPSS statistical software (Chicago, IL, USA, version 24). A $p < 0.05$ was considered a significant difference.

Results

Table 2 shows the Pearson correlation coefficients between the study variables. The frequency of the M55 allele is positively associated with the prevalence ($r = 0.499$, $df = 38$, $p = 0.001$) and mortality ($r = 0.414$, $df = 38$, $p = 0.008$) of COVID-19. However, the allelic frequency of R192 was not associated with the prevalence and mortality.

It should be noted that the prevalence of COVID-19 was significantly associated with HDI ($r = 0.368$, $df = 46$, $p = 0.010$) and test ($r = 0.306$, $df = 46$, $p = 0.035$). There was significant relationship between HDI and the allelic frequency of R192 ($r = 0.297$, $df = 46$, $p = 0.040$). Therefore, it seems that HDI and the number of performed test per 10^6 people act as possible confounders. In order to statistically rule out the influence of these variables on the associations between prevalence/mortality of COVID-19 and the allelic frequencies, the partial correlation coefficients were calculated. As it is summarized in Table 3, the frequency of M55 was positively correlated with the prevalence (partial $r = 0.487$, $df = 36$, $p = 0.002$) and mortality of COVID-19 (partial $r = 0.551$, $df = 36$, $p < 0.001$), after adjustments for possible confounders. It means that countries with higher M55 frequency have higher prevalence/mortality of COVID-19. It should be noted that the R192 allelic frequency was not correlated with the prevalence/mortality of COVID-19 (Table 3).

Discussion

Current results reveal that the allelic frequency of M55 is positively associated with the prevalence and mortality of COVID-19 (Tables 2 and 3). This is in very good agreement with the decrease of paraoxonase activity in the M55 variant,[10] rise of oxidative stress in COVID-19,[18–20] and reduction of serum PON1 activity in septic patients.[14]

A meta-analysis indicates that hypertension raises the risks of severity and fatality of COVID-19.[26,27] The inverse association between PON1 activity and the risk of cardiovascular and inflammatory diseases has been reported previously.[9,28,29] It might be concluded that low activity of PON1 is a common risk factor for susceptibility to hypertension and for risk of mortality due to COVID-19 in hypertensive patients.

In current pandemic, men are significantly more likely to die than women.[29–31] It is worth noting that serum paraoxonase activity is higher in females.[32] Age of patients and co-morbidities are significant predictors of mortality due to COVID-19.[27,30,31] Surprisingly, this is may also be explained by the reducing of serum PON1 activity with age and the association between low PON1 activity and the risk of cardiovascular disease.[9,28]

In previous pandemics and in the current COVID-19 pandemic, ethnicity has been involved.[31] Prevalence and mortality of COVID-19 are lower in East Asians compared with Caucasians. Actually, ethnicity has a very complex nature. Ethnic groups have many differences with each other in their gene pools and environmental factors such as socioeconomic factors and cultural behaviors. The variations in the PON1 activity, which are attributed to both L55M and Q192R polymorphisms, are greater among Caucasians than

Table 1. Prevalence, mortality, and amount of accomplished diagnostic tests of COVID-19 in 48 countries, the allelic frequency of the *PON1* L55M and Q192R polymorphisms, and Human Development Index in the study.

Country	Prevalence (per 106 population)	Mortality (per 106 population)	Number of COVID-19 diagnostic tests performed (per 106 population)	Allelic frequency M55 (%)	Allelic frequency R192 (%)	HDI
Argentina	30,651	831.0	82,498	32.51	27.59	0.830
Australia	1087	35.0	383,743	36.99	26.79	0.938
Austria	28,859	295.0	327,955	35.67	25.48	0.914
Benin	243	4.0	24,003	NA	61.22	0.520
Brazil	28,930	801.0	102,736	27.29	42.27	0.761
Canada	9174	309.0	292,823	6.13	43.06	0.922
Chile	28,364	789.0	267,884	NA	39.64	0.847
China	60	3.0	111,163	7.11	52.64	0.758
Costa Rica	26,310	327.0	74,614	NA	24.32	0.794
Cuba	709	12.0	93,742	35.04	36.92	0.778
Czech	47,141	710.0	277,749	43.17	46.36	0.891
Denmark	12,793	138.0	1215761	38.00	30.00	0.930
Dominican	12,798	213.0	63,418	26.45	50.24	0.745
Egypt	1107	64.0	9699	39.99	38.57	0.700
Estonia	7944	73.0	341,449	35.89	24.80	0.882
Ethiopia	923	14.0	13,868	NA	40.83	0.470
Finland	4086	70.0	335,209	38.68	25.01	0.925
France	33,216	775.0	307,641	36.54	29.69	0.891
Germany	11,726	183.0	332,083	33.51	27.93	0.939
Greece	9353	183.0	220,207	36.55	23.52	0.872
Hungary	19,241	426.0	160,441	25.45	33.33	0.845
India	6689	98.0	97,326	18.65	36.56	0.647
Iran	10,594	547.0	70,042	50.81	34.22	0.797
Ireland	14,352	410.0	385,411	27.48	29.75	0.942
Italy	24,507	861.0	346,809	43.63	26.85	0.883
Japan	1072	16.0	26,373	6.59	53.66	0.915
Malaysia	1839	11.0	79,226	28.37	31.55	0.804
Mexico	8188	793.0	21,185	20.11	49.48	0.767
Morocco	9074	149.0	103,934	27.00	23.50	0.676
The Netherlands	29,076	531.0	227,047	37.12	29.13	0.933
Peru	28,787	1078.0	150,284	NA	46.07	0.759
Poland	24,436	396.0	160,019	36.90	26.06	0.872
Portugal	26,904	405.0	427,235	60.81	29.73	0.850
Qatar	49,096	84.0	389,137	32.90	38.00	0.848
Saudi Arabia	10,164	166.0	268,384	NA	26.47	0.857
Serbia	16,119	151.0	192,870	32.00	28.05	0.799
Singapore	9915	5.0	757,916	7.19	60.94	0.935
South Africa	13,010	356.0	89,838	NA	36.83	0.705
South Korea	619	10.0	57,839	5.58	55.73	0.906
Spain	34,700	942.0	468,697	41.66	30.42	0.893
Sweden	22,768	647.0	287,821	39.80	25.30	0.937
Switzerland	35,653	506.0	302,224	58.94	25.86	0.946
Thailand	56	0.9	13,995	4.97	34.72	0.765
Tunisia	7693	251.0	37,005	32.42	16.89	0.739
Turkey	5522	152.0	209,360	35.39	37.57	0.806
United Kingdom	22,887	831.0	615,299	36.24	28.25	0.920
Ukraine	15,171	263.0	97,271	NA	34.96	0.750
USA	39,598	808.0	560,928	37.96	28.10	0.920

References: [10,33–65].

Table 2. Correlation between epidemiologic parameters of COVID-19 and study variables.

	Prevalence		Mortality	
Variable	r	P	R	P
M55 allelic frequency*	0.499	0.001	0.414	0.008
R192 allelic frequency	−0.243	0.096	−0.162	0.270
HDI	0.368	0.010	0.246	0.092
Test	0.306	0.035	0.131	0.376

Note: Degree of freedom (df) for all correlations are 44, except for correlations shown by * which is 38.

Table 3. Partial correlation between epidemiologic parameters and allelic frequency of study polymorphisms after adjusted for Human Development Index and amount of accomplished diagnostic test (per 10^6 people).

	Prevalence		Mortality	
Variable	R	P	R	P
M55 allelic frequency*	0.460	0.004	0.397	0.014
R192 allelic frequency**	−0.149	0.322	−0.097	0.521

Note: Degree of freedom (df) for correlations shown by * and ** are 36, 44 respectively.

Asians and Africans.[10] Taken together, at least in part, allelic frequency and effects of ethnicity-related factors on the PON1 activity may explain the difference in mortality and prevalence of COVID-19 between Eastern and Western countries. Taken together, the MM homozygous individuals showed considerably lower PON1 enzyme activity and the reduction in PON1 activity is greater among Caucasians than Asians and Africans.[10] Serum paraoxonase activity is higher in females,[32] and PON1 activity is negatively correlated with age.[9,28] These facts may predict, at least in part, different prevalence/mortality of COVID-19 between ethnicities, age, and gender groups.

Finally, a major limitation of the present study should be acknowledged. We know that the rs662 and rs854560 polymorphic sites and other polymorphisms of the *PON1* have strong linkage disequilibrium with each other.[66] In this study, the allelic frequencies in countries were estimated using published articles. However, there were no data on haplotypic frequencies in those articles. The present study is an ecological study, and it cannot be judged that people who carry the M55 allele of the rs854560 polymorphism are more susceptible to be infected by SARS-CoV-2 or have higher mortality rates due to COVID-19 than the carriers of the L55 allele. Therefore, in the interpretation of the present findings, care must be taken not to fall into the trap of ecological fallacy. However, it should be noted that there are some genetic association studies using case-control design[67,68] which confirmed findings of previous ecologic studies.[22,25] In order to generalize the findings of the present study at the individual level, further observational studies (such as case-controls and cohorts) are necessary to examine gene-environment interactions and combinations of polymorphisms in susceptibility to and outcome of COVID-19.

Conclusions

The present ecological study analyzed data of prevalence and mortality of COVID-19 from 48 countries. Statistical analysis revealed that the allelic frequency of M55 is positively correlated with the mortality of COVID-19. This means that countries with higher M55 frequency have higher prevalence and mortality of COVID-19.

Author's contributions

The author has reviewed the literature, data collection, analyzed the data, summarized the findings, and written the manuscript.

Declaration of conflicting interests

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Availability of data and materials

Data were presented in Table 1 of the manuscript.

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