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# The morbidity and mortality of COVID-19 are correlated with the Ile105Val glutathione S-transferase P1 polymorphism

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## Abstract

**Background:** Oxidative stress is an important issue in coronavirus disease 2019 (COVID-19). Considering that glutathione S-transferase P1 (*GSTP1*) is involved in cellular detoxification, it may play an important role in susceptibility to infection with SARS-CoV-2 and/or its outcome. In the present study, the association between the Ile105Val *GSTP1* polymorphism (rs1695) and susceptibility to SARS-CoV-2 infection, as well as its outcome was investigated. Data on the prevalence (per 10<sup>6</sup> people), case-fatality (per 100 infected cases), and mortality (per 10<sup>6</sup> people) of COVID-19 and various potential confounders (the life expectancy at birth, density of medical doctors, density of nursing and midwifery personnel, and the gross national income per capita) were used. The latest data available for 45 countries were used for the study.

**Results:** In multivariate linear regression analyses, the Val105 allelic frequency showed positive association with the log-prevalence (partial  $r = 0.308$ ,  $p = 0.042$ ) and log-mortality of COVID-19 (partial  $r = 0.316$ ,  $p = 0.037$ ). The log-fatality did not show association with the allelic frequency. In the next step, only countries with the gross national income per capita more than \$15,000 were included in the analysis. In the selected countries, the frequency of Val105 was positively associated with the log-prevalence (partial  $r = 0.456$ ,  $p = 0.009$ ) and log-mortality of COVID-19 (partial  $r = 0.544$ ,  $p = 0.001$ ).

**Conclusions:** The present findings indicate that countries with higher Val105 allelic frequency of the rs1695 polymorphism showed higher prevalence and mortality of COVID-19.

**Keywords:** Ecologic study, Epidemiologic measures, Pandemic

## Background

Numerous gene families, including glutathione S-transferases (GSTs) superfamily, are involved in cellular detoxification process and neutralizing oxidative stress. The *GSTP1* (MIM: 134660, belong to class pi) has many genetic variations in human. A missense variant A/G (rs1695) in exon 5 of the *GSTP1* result in amino acid substitution Ile105Val. The stability of the Val105 form is less than the other form [1]. This alteration decreased the *GSTP1* enzyme activity [2–4].

The *GSTP1* is expressed in all tissues and cells, including lung epithelial cells and lung-resident macrophages [5–7]. In occupationally di-isocyanate-induced asthma,

the Val105 allele is positively associated with the bronchial hyperreactivity [8]. Exposure to high “diesel exhaust particle” increased the risk of wheezing phenotypes only among the carriers of the Val105 allele (Ile/Val and Val/Val genotypes) [9]. Children with the Val/Val genotype had slower lung function growth than the other genotypes [10]. Downregulation of the *GSTP1* mRNA level and lower total GST activity were reported in a mouse model of asthma following allergen challenge [11]. Taken together, it is concluded that the *GSTP1* has a central role in lung function.

Coronavirus disease 2019 (COVID-19) is a contagious disease; therefore, its prevalence (per 10<sup>6</sup> people), case-fatality (per 100 infected cases), and mortality (per 10<sup>6</sup> people) may be affected by various social factors, such as the life expectancy at birth, country income, etc. Very

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**Table 1** Correlation between log-transformed of epidemiologic parameters and selected risk factors

Variables	Log-Prevalence		Log-Mortality		Log-Fatality	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>p</i>
Log-GNI per capita	0.406	0.006	0.349	0.019	0.065	0.673
Log-number of COVID-19 diagnostic tests performed (per 10 <sup>6</sup> people)	0.443	0.002	0.241	0.111	- 0.159	0.297
Life expectancy at birth (years)	0.091	0.551	0.187	0.220	0.193	0.204
Density of medical doctors (per 10 <sup>4</sup> people)	0.384	0.009	0.393	0.008	0.162	0.287
Density of nursing and midwifery personnel (per 10 <sup>4</sup> people)	0.288	0.055	0.251	0.096	0.048	0.752

\*Degree of freedom (df) for all correlations is 43

recently some investigators suggested that some genetic polymorphisms might be involved in susceptibility to genetic polymorphisms or outcome of the disease [12–16].

Oxidative stress is an important issue in COVID-19 [17–19]. Considering that GSTP1 is involved in cellular detoxification and it has important role in lung function, it is suggested that GSTP1 plays an important role in susceptibility to SARS-CoV-2 infection and/or its outcome. Very recently, association between some genetic polymorphisms and morbidity/mortality of COVID-19 were reported [12–16]. A study showed that the COVID-19 mortality and case-fatality are associated with the *GSTT1* polymorphism [12]. There are no data on the association between COVID-19 epidemiologic parameters and the rs1695. These facts sufficiently provide us with a theoretical hypothesis to carry out the present study.

## Methods

In this study, the life expectancy at birth (LE), density of medical doctors, density of nursing and midwifery personnel, and the gross national income (GNI) per capita (PPP international \$) as the indices for economic situation and health services in different countries were considered as the potential risk factors for susceptibility

to COVID-19 or the disease outcome. The latest data available for countries were achieved from the World Health Organization website [www.who.int/countries/en/](http://www.who.int/countries/en/). The latest data for GNI per capita for countries were obtained from the World Bank data (<https://data.worldbank.org/indicator/NY.GNP.PCAP.PP.CD>).

The number of COVID-19 diagnostic tests performed per one million population in each country was also used as another risk variable. Data for the prevalence, fatality, mortality, and level of performed diagnostic test of COVID-19 on July 7, 2020, were achieved from the website [www.worldometers.info/coronavirus/countries](http://www.worldometers.info/coronavirus/countries). The Val105 allelic frequency in different countries was obtained from previous reports (Table S1 in supplement file). Data from 45 countries were included in the analysis. Data from Argentina, Australia, Brazil, Bulgaria, Canada, China, Colombia, Czech, Denmark, Egypt, Finland, France, Germany, Hungary, Iceland, India, Iran, Iraq, Italy, Jamaica, Japan, Jordan, Kazakhstan, Lebanon, Mexico, Moldova, Morocco, Netherland, Norway, Poland, Portugal, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovenia, South Africa, South Korea, Spain, Sweden, Thailand, Turkey, the UK, and the USA were included in the analysis.

Variables were checked for their normality by one-sample Kolmogorov-Smirnov test. Non-normally

**Table 2** Multivariable linear regression analysis for associations of log-mortality and log-prevalence of COVID-19 with the frequency of the Val105 allele in the various countries around the world

Variables	Unstandardized coefficients		Standardized coefficients beta	Partial correlations	<i>t</i>	<i>P</i>
	<i>B</i>	Std. Error				
Log-prevalence as dependent variable						
Constant	- 1.067	1.231	-	-	- 0.867	0.391
Log-GNI per capita	0.815	0.262	0.407	0.424	3.034	0.004
Val105 allelic frequency	0.020	0.009	0.281	0.308	2.094	0.042
Log-mortality as dependent variable						
Constant	- 3.2348	1.648	-	-	- 1.971	0.055
Log-GNI per capita	0.918	0.359	0.350	0.367	2.553	0.014
Val105 allelic frequency	0.027	0.013	0.296	0.316	2.156	0.037

The first model was significant with  $F = 6.76$ ;  $df = 2, 42$ ;  $P = 0.003$ ; adjusted  $R^2 = 0.207$ . The second model was significant with  $F = 5.55$ ;  $df = 2, 42$ ;  $P = 0.007$ ; adjusted  $R^2 = 0.171$

**Table 3** Correlation between log-transformed of epidemiologic parameters and possible confounders in selected countries with GNI-per capita more than \$15,000

Variables	Log-Prevalence		Log-Mortality		Log-Fatality	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>p</i>
Log-GNI per capita	0.527	0.001	0.353	0.041	- 0.084	0.637
Log-number of COVID-19 diagnostic tests performed (per 10 <sup>6</sup> people)	0.541	0.001	0.261	0.136	- 0.230	0.190
Life expectancy at birth (years)	0.141	0.426	0.240	0.171	0.191	0.278
Density of medical doctors (per 10 <sup>4</sup> people)	0.469	0.005	0.461	0.006	0.139	0.434
Density of nursing and midwifery personnel (per 10 <sup>4</sup> people)	0.243	0.166	0.172	0.332	- 0.030	0.866

Degree of freedom (df) for all correlations is 32

distributed variables (prevalence, mortality, case-fatality rates, and number diagnostic test performed per 10<sup>6</sup> people) were log-transformed.

Variables with  $p \leq 0.1$  in the univariable analysis were introduced into the multivariable models. Only two different models were fitted for combination of the epidemiologic parameters with the rs1695 polymorphism. The log-transformed variables were considered as outcome variables, and the allelic frequency and the risk factors were introduced into the model as explanatory variables. A backward removal method was used for each model construction. Analyses were performed using the SPSS statistical soft-ware (Chicago, IL, USA, version 24). A  $p < 0.05$  was considered statistically significant difference

## Results

In univariate analysis, the frequency of the Val105 allele showed no significant correlations with the log-prevalence ( $r = 0.331$ ,  $df = 44$ ,  $p = 0.025$ ), log-mortality ( $r = 0.363$ ,  $df = 44$ ,  $p = 0.013$ ), and log-fatality ( $r = 0.175$ ,  $df = 44$ ,  $p = 0.244$ ) of the COVID-19.

Table 1 shows the association between potential risk factors and the log-transformed of prevalence, mortality, and case-fatality of COVID-19. Variables with  $p \leq 0.1$  in the univariable analysis were used in multivariable linear regression analyses (Table 1).

Two different models were fitted for combination of prevalence and mortality with the rs1695 polymorphism. The log-prevalence and log-mortality were considered as outcome variables, and the Val105 allelic frequency and the risk factors were introduced into the model as explanatory variables.

Results of multivariate analysis are summarized in Table 2. Based on multivariate analyses, the frequency of Val105 was positively associated with the log-mortality (partial  $r = 0.316$ ,  $p = 0.037$ ) and log-prevalence of COVID-19 (partial  $r = 0.308$ ,  $p = 0.042$ ).

In next step, only countries with the gross national income (GNI) per capita (PPP international \$) more than \$15,000 were included in the analysis. Table 3 summarizes the associations between the risk factors and the log-transformed of epidemiologic parameters of COVID-19 in the selected countries. The results of multivariate

**Table 4** Multivariable linear regression analysis for associations of log-mortality and log-prevalence of COVID-19 with the frequency of the Val105 allele in the various countries around the world in selected countries with GNI-per capita more than \$15,000

Variables	Unstandardized coefficients		Standardized coefficients beta	Partial correlations	<i>t</i>	<i>P</i>
	<i>B</i>	Std. Error				
Log-prevalence as dependent variable						
Constant	- 4.790	1.717	-	-	- 2.789	0.009
Log-test	0.429	0.194	0.319	0.374	2.209	0.035
Log-GNI per capita	1.118	0.417	0.384	0.440	2.681	0.012
Val105 allelic frequency	0.028	0.010	0.360	0.456	2.806	0.009
Log-mortality as dependent variable						
Constant	- 5.979	2.463	-	-	- 2.427	0.021
Log-GNI per capita	1.344	0.530	0.358	0.415	2.537	0.016
Val105 allelic frequency	0.051	0.014	0.509	0.544	3.606	0.001

The first model was significant with  $F = 10.726$ ;  $df = 3, 30$ ;  $P < 0.001$ ; adjusted  $R^2 = 0.469$ . The second model was significant with  $F = 9.63$ ;  $df = 2, 31$ ;  $P < 0.001$ ; adjusted  $R^2 = 0.344$

analysis are summarized in Table 4. In the selected countries, the frequency of Val105 was positively associated with the log-prevalence (partial  $r = 0.456$ ,  $p = 0.009$ ) and log-mortality of COVID-19 (partial  $r = 0.544$ ,  $p = 0.001$ ).

## Discussion

The main findings of the present study are that the frequency of Val105 was positively associated with the log-prevalence and log-mortality of COVID-19. It means that countries with higher Val105 allelic frequency showed higher prevalence of COVID-19 and mortality due to COVID-19. The present findings may explain, at least in part, some differences in COVID-19 mortality between East Asian and European populations by the Val105 allelic frequency.

Numerous facts are indicated that GSTP1 plays an important role in lung function [5, 8–11, 20]. GSTP1 has pleiotropic properties; it binds directly to c-Jun N-terminal kinases and acts as a negative regulator. It also has a negative regulatory role in regulating tumor necrosis factor- $\alpha$  (TNF $\alpha$ )-induced MAPK signaling. These functions are independent from its enzyme activity [21].

It is widely acknowledged that the mortality due to severe respiratory problems in patients infected by SARS-CoV-2 is high [22]. On the other hand, COVID-19 is associated with oxidative stress [17, 18]. It is suggested that COVID-19 mortality might be associated with oxidative stress and/or SARS-CoV-2-activated cytokine storm syndrome. Both of these phenomena might be interpreted with the pleiotropy properties of GSTP1.

It is worth mentioning that the Val105 form compared to the other form has lower detoxification activity; therefore, COVID-19 patients, who are carriers of Val105, often experience severe oxidative stress compared to the Ile/Ile genotype. This may lead to severity of the disease and subsequently death due to COVID-19 in the carriers of Val105.

A literature review indicated that COVID-19 has affected more males than females, and also male gender significantly increases the case fatality [23, 24]. This difference, at least in part, may be explained by the sexual dimorphisms of GSTP1 enzyme activity. The enzyme activity is higher in females than males [25]. Several observational and experimental studies should be carried out to approve the present findings and the abovementioned hypotheses.

## Conclusions

The present findings indicate that countries with Val105 higher allelic frequency of the rs1695 polymorphism showed higher prevalence and mortality of COVID-19.

## Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s43042-020-00094-0>.

**Additional file 1: Table S1.** Prevalence, mortality and case-fatality of COVID-19 in 46 countries, the genotypic frequency of the GSTP1 Ile105Val polymorphism and other variables used in the study

## Abbreviations

COVID-19: Coronavirus disease 2019; df: Degree of freedom; GSTP1: Glutathione S-transferase P1; GNI: Gross national income

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## Author's contributions

Study design, data collection, data analysis, and writing the article are done by MS. The author read and approved the final manuscript.

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All data generated or analyzed during this study are included in this published article and its supplementary information file.

## Ethics approval and consent to participate

None

## Consent for publication

None

## Competing interests

None

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