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COVID-19 Spreading Across World Correlates with *677T* Allele of the Methylenetetrahydrofolate Reductase (*MTHFR*) Gene Prevalence

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Abstract

Homocysteine assessment has been proposed as a potential predictive biomarker for the severity of COVID-19 infection. The purpose of this review was to analyze the correlation between the prevalence of *MTHFR 677T* allele and COVID-19 incidence and mortality worldwide. There is a clear trend towards the worldwide prevalence of *MTHFR 677T* allele and COVID-19 incidence and mortality. The prevalence of *MTHFR 677T* allele in the Latino population and the incidence and mortality for COVID-19 was higher for this ethnic group than that reported for most other populations globally. Statistical analysis showed a relatively strong correlation between *677T* allele and death from coronavirus. Genetic polymorphism of *MTHFR C677T* may modulate the incidence and severity of COVID-19 pandemic infection.

Keywords: Homocysteine • *MTHFR* gene • *MTHFR 677T* mutation prevalence • *MTHFR C677T* polymorphism • COVID-19 vulnerability

Introduction

Since the beginning of the novel coronavirus pandemic, caused by the viral pathogen COVID-19, the medical and scientific community is facing challenges for managing patients and identifying reliable biomarkers related to disease progression, in order to promptly stratify patients for their risk of critical manifestations. Trustworthy biomarkers would be helpful for screening, clinical management, and prevention of serious complications. In the absence of specific treatment and vaccine for the COVID-19, there is an urgent need to find markers that predict severe outcomes for patients with a confirmed or suspected COVID-19 diagnosis. It is crucial to identify clinical, epidemiological and laboratory markers for one of the main causes of mortality, especially regarding the damage to microvasculature which can potentially be modifiable by safe therapeutic interventions.

At present, there are over 25 million confirmed COVID-19 cases with 900 thousand deaths. Looking the worldwide epidemiologic data, there are remarkable differences among countries regarding COVID-19 infection rates and mortality, especially comparing very high data relative to United States of America or South America and sub-Saharan Africa or Finland, where incidence and mortality appear remarkably low (WHO Coronavirus Disease (COVID-19) Dashboard https://COVID-19.who.int/). This simple epidemiological observation represents the base for searching genetic differences among populations or ethnicities which may explain different clinical manifestations of COVID-19 infection [1,2].

In addition to serological and clinical biomarkers that are clearly correlated with a severe clinical course of COVID-19 infection [3,4] the role of Homocysteine (Hcy) as an important prognostic marker has been recently hypothesized [5]. The role of Hcy in several metabolic and inflammatory processes has already been demonstrated, and different populations with different ethnical predominances show different prevalences for *MTHFR* gene mutations and *MTHFR* activities [6]. The population frequency of *677T* allele homozygosity ranges from 1% or less among Blacks from Africa and the Finnish population to 20% or more among Latino and US Hispanics. Intriguingly, the world distribution of *MTHFR C677T* polymorphism has a high degree of heterogeneity following a geographical gradient of south-north and west-east both in Europe and Americas [7-9].

Homocysteine has been under a lot of speculation since its discovery in 1932 [10]. It is known that a high plasma level of homocysteine significantly increases the incidence of vascular damage in both small and large vessels [10,11]. Hyperhomocysteinemia has neurotoxic, neuroinflammatory, neurodegenerative, proatherogenic, prothrombotic and prooxidative effects [12]. Homocysteine concentrations above the 90th percentile are associated with increased risk of degenerative and atherosclerotic processes [13] in the coronary, cerebral and peripheral circulatory system. In this regard, determining homocysteine together with other cardiovascular risk markers (Apo B, Lp (a), LDL, fibrinogen, PAI-1) now is implemented in the clinical practice [14]; moreover, recent evidence suggests the role of homocysteine as a risk factor for thromboembolism, given its effect on platelet reactivity [15].

Homocysteine has been found to be a predictor of disease progression in 273 patients with mild COVID-19 disease in Shanghai: 72 of the patients showed disease progression as assessed by lung CT scan. More than 40 parameters were measured in these 273 patients at admission of which only age, homocysteine and monocyte-to-lymphocyte ratio (MLR) were found as significant predictors of disease progression as shown by CT changes in the

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lung. Patients with hyperhomocysteinemia (>15.4 μmol/L) had a three-fold increased risk of CT changes progression. Of the three predictor markers, only homocysteine is readily modifiable. Very recent data witnessed a predictive value of Hcy (together with age, MLR, and period from disease onset to hospital admission) for severe pneumonia on chest CT at first week from COVID-19 patients, but did not report additional organ involvement [5].

It is known that homocysteine is an efficacious biomarker of cardiovascular risk, even though cardiovascular complications are critical in hospitalized COVID-19 patients Hcy has not yet been adopted to be used for the stratification of COVID-19 patients and it has not been included in prospective studies focused on laboratory markers useful for the clinical evaluation of the COVID-19 patients. To our knowledge, till today, no evidences have been published about the *MTHFR* gene polymorphisms that are clearly implicated into a defective Hcy metabolism and COVID-19 disease. The purpose of our research was to illustrate the relationship between the prevalence of the genetic polymorphisms of *MTHFR C677T* and COVID-19 incidence and mortality rates, demonstrating that COVID-19 incidence and mortality rates are strongly correlated to the prevalence of *MTHFR* 677C>T mutation which is linked explicitly to pro-thrombotic events due to altered homocysteine metabolism.

Materials and Methods

Data regarding *MTHFR* status, regarding *MTHFR* 677C>T gene mutation, were obtained from the interrogation of the Genome Aggregation Database (genomAD) which is publicly available from the web"https://gnomad.broadinstitute.org." COVID-19 cases, including prevalence and mortality, were obtained from "https://www.worldometers.info/coronavirus" 27th August 2020.

MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) was used to perform statistical analysis. Correlation analysis was used to determine whether the values of two variables are associated. The correlation expresses the degree that, on an average, two variables change correspondingly. If one variable increases when the second one increases, then there is a positive correlation. In this case, the correlation coefficient will be closer to 1.

The P-value is the probability that the current result to be found if the correlation coefficient were, in fact zero (null hypothesis). If this probability is lower than the conventional 5% (P <0.05) the correlation coefficient is called statistically significant.

Correlations between the measured variables in each group were analyzed using Pearson's correlation method. All statistical tests were performed at a significance level (α) of 0.05.

Results

The analysis examined their associations for the allele frequency with cases of coronavirus COVID-19 death and incidence for the polymorphisms. Subgroup analyses were stratified by ethnicity (Table 1). Officially reported COVID-19 cases and the number of COVID-19 related deaths were stratified according to the ethnic groups as well (Table 1).

A correlation between *MTHFR 677T* allele prevalence and COVID-19 incidence and mortality rates can be clearly observed if data were stratified for different ethnic groups, demonstrating the presence of a gradient with South-North and East-West directions worldwide. The frequency of *MTHFR 677T* allele in the Latino population (50%) was higher than that reported for most of the other populations in the world, similarly coronavirus death correlation with the frequency of this allele in most of the other populations was lower (Finnish, African sub-Saharan, etc.) (Figures 1 and 2). Correlation analysis showed a relatively strong correlation between *677T* allele and death coronavirus with 85%, p=0.03. The correlation between the allele frequency and coronavirus mortality was found very high (85%) (Figures 3 and 4).

Discussion

The relationship between the prevalence of the genetic polymorphisms of *MTHFR C677T* and COVID-19 incidence and mortality rates seems to be intriguing. It may be a useful biomarker to stratify COVID-19 infection severity and can be used for preventive medical treatments and supplementations.

The correlation between Hcy level and COVID-19 severity of infection has been recently demonstrated, [4,5] currently under our evaluation in a cohort of 313 patients affected by COVID-19 infection which confirms the significant correlation between blood Hcy > 16 μmol/L and severe prognosis or mortality.

Several studies have clarified the pathogenic correlation between COVID-19 infection and Hcy metabolism. Recently, it has been described the novel regulatory mechanisms directly involved with Hcy that activates the angiotensin II type receptor [16,17]. Ferroptosis, a newly identified form of regulated cell death, is characterized by iron and lipid reactive oxygen species (ROS) accumulation and smaller mitochondria with condensed mitochondrial membrane densities. Still, it does not share morphological, biochemical, or genetic similarities with other forms of regulated cell death, such as apoptosis [18]. Increasing evidence suggests that ferroptosis dysfunction is positively related to various human diseases, including tumorigenesis [19]. Ferroptosis was found to be linked to neurological disturbances, including cognitive impairment [20], ageusia, and anosmia (taste and smell loss) [21,22] that are common manifestations of COVID-19 disease.

The SARS-CoV-2 may involve the transfer of methyl group for viral RNA capping from the host cell synthesized S-adenosylmethionine (SAM). The latter is converted into S-adenosylhomocysteine (SAH), which further in the presence of SAH hydrolase (SAHH) removes adenosine, and produces an intermediate product called "homocysteine," which is recycled by remethylation and trans-sulphuration pathway in the human body [23].

Regarding the genetic background of Hcy metabolisms, the enzyme 5,10-methylenetetrahydrofolate reductase (*MTHFR*) is involved in the folate metabolism. The *MTHFR* converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate which produces methyl donor for the conversion of homocysteine to methionine [24].

The *MTHFR* gene is located on chromosome 1 (1p36.3), and two common alleles, the *677T* (thermolabile) allele and the A1298C allele, have been described. The population frequency of *677T* homozygosity ranges from 1% or less among Blacks from Africa and the United States to 20% or more among Italians and US Hispanics. *677T* homozygosity in infants is associated with a moderately increased risk for spina bifida (pooled odds ratio = 1.8; 95% confidence interval: 1.4, 2.2).

Table 1. c.677C>T p.Ala222Val rs1801133 damaging.

	677C>T p.Ala222Val rs1801133				Corona virus			
Population	**Allele count**	**Allele Number**	**Number of Homozygotes**	**Allele Frequency**	**Total Cases**	**Total Deaths**	**Tot Cases /1 M pop**	**Deaths /1 M pop**
Latino	17788	35440	4654	0.5019	2899134	105354	6729	245
European (non-Finnish)	43635	129108	7511	0.338	2574301	196444	2136	204
East Asian	5790	19944	929	0.2903	119264	5912	73	4
European (Finnish)	5799	25116	694	0.2309	7295	329	1317	59
South Asian	4443	30616	389	0.1451	2888739	65492	974	22
African	2714	24970	158	0.1087	599849	13315	447	10

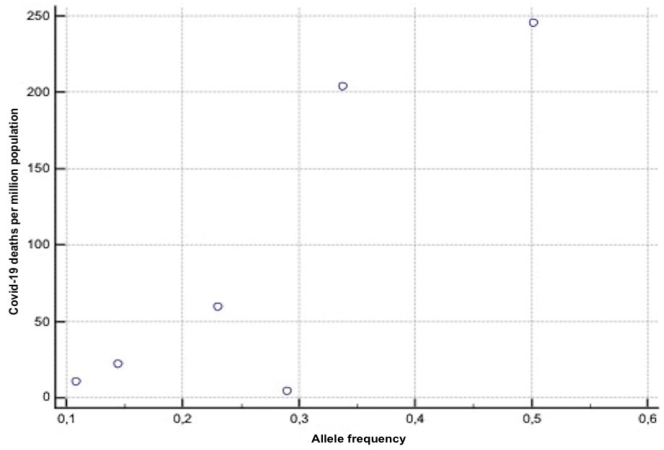

Figure 1. The relationship between allele frequencies of 677C>T and coronavirus deaths/1M pop was represented graphically by a scatter diagram.

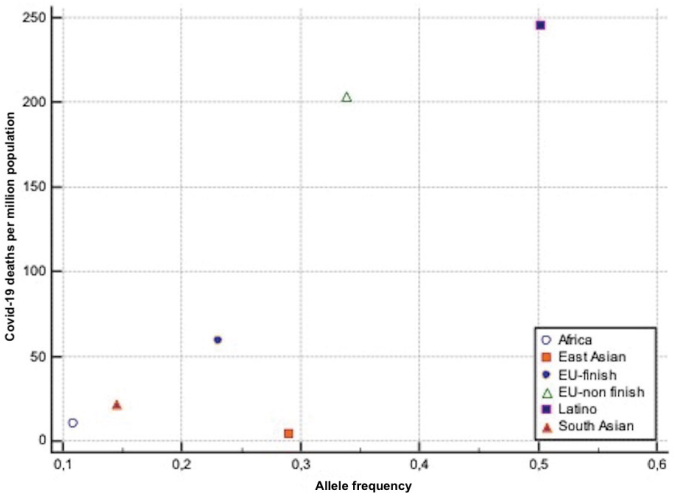

Figure 2. The relationship between allele frequencies of 677C>T and coronavirus deaths/1M pop was represented graphically by a scatter diagram, stratified by ethnicity.

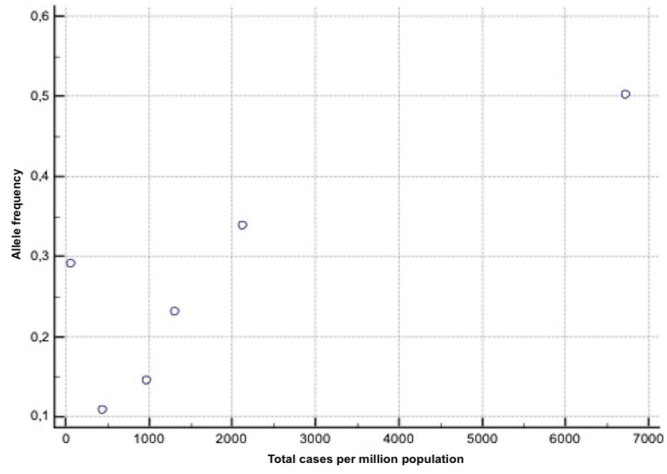

Figure 3. The relationship between allele frequencies of C677T and coronavirus total cases/1M pop was represented graphically by a scatter diagram.

The *677T* allele is characterized by a point mutation at position 677 of the *MTHFR* gene that converts a cytosine (C) into a thymine (T); this mutation results in an amino acid substitution (alanine to valine) in the enzyme. The *677T* allele homozygous mutated subjects have higher increased blood homocysteine levels while the heterozygous mutated subjects have mildly raised homocysteine levels compared with the normal, non-mutated controls [6].

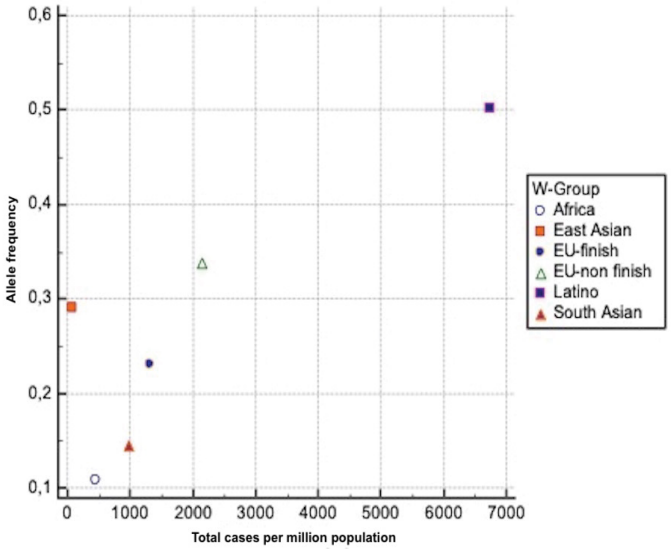

Figure 4. The relationship between allele frequencies of C677T and coronavirus cases/1M pop was represented graphically by a scatter diagram, stratified by ethnicity.

The population frequency of the *677T* allele showed regional and ethnic variations (Table 1). For example, the allele frequency was high in Italy and among Hispanics living in California and was low among US Blacks and in some areas of sub-Saharan Africa. The frequency of *677T* homozygosity showed similar variability [25]. Amongst the European, the homozygous allele was found highest in the Italians and lowest in the Germans [26-28]. The prevalence of the homozygous TT genotype was 10-12% in Europe's several areas (for example, Spain, France, and Hungary). In Britain, the percentage of homozygosity in the population was approximately 13%. However, the prevalence appeared to be lower (4% and 6%, respectively) in Finland, Helsinki, and the northern Netherlands. In contrast, in some southern European areas, it was much higher (26% and 20% in Campania and Sicily, respectively). In the Americas, the frequency of the homozygous TT genotype was more elevated in Mexico (32%), intermediate in Atlanta (11% among whites), and somewhat lower in Alberta (6%). For the Blacks living in America and Brazil, the frequency of homozygosity was very low (1 or 2% only) [29-31].

In Australia, TT prevalence was 7.5% among whites. Among the Whites not within Europe, the homozygous mutation percentages ranged from 10 to 14% in countries like Canada, America, Brazil, and Australia [32-34]. Zero rates was found on the homozygosity of the sub-Saharan African population.

The several fold variations in the prevalence of the TT homozygous genotype across the study areas were also consistent, in some areas, with the presence of geographical gradients. In Europe, for example, the prevalence of the TT genotype increased in a roughly southerly direction, from low values in the north (4-7% in Finland, Helsinki, northern Netherlands, and Russia), to intermediate values (8-10%) in France and Hungary, to higher values in southern Europe (12-15% in Spain and northern Italy), peaking in south Italy (20-26% in Campania and Sicily). In North America, TT homozygotes' frequency increased from western Canada (Alberta) to the southeastern United States (Atlanta) and peaked in Mexico [7].

The comparison of the prevalence of the homozygousity for *MTHFR 677T* mutated allele and the incidence and mortality by COVID-19 showed a high degree of correlation, especially regarding South-North and East-West gradients, as well as for Americans, Europeans, and Asians populations. This data could be traced back to ancestral migratory phenomena related to population genetic or to a reduced dietary intake of B9 (folic acid) and other B-vitamins that could characterize different dietary regimens among different cultures [35].

The genetic data related to *MTHFR* status coupled with Hcy dosage could represent important information for the assessment and stratification of COVID-19 patients. In association with other epidemiologic, hematologic, biochemical and functional parameters, these data could be useful to define

better population-based risk strategies to fight COVID-19 infection and lethality. It has been demonstrated that the presence of *MTHFR 677T* may result in the need for a higher folate and B-vitamins intake to maintain normal Hcy levels; therefore, a preventive therapeutic integration of Folic acid and B-vitamins could result in the reduction of prevalence and mortality for COVID-19 viral infection [36-39].

Conclusion

In conclusion, Genetic polymorphism of *MTHFR 677T* may modulate the risk of COVID-19 incidence and severity.

Population data on correlation between the *677T* allele and COVID-19 incidence and mortality would be very useful in regional and national management strategy and might help the population and public health geneticists to assess the potential impact of preventive measures based on environmental modifications. Some adverse biochemical effects of the thermolabile enzyme coded by the T allele, such as the increase in total plasma homocysteine, appear to be reversible by increasing the consumption of the vitamin B and folic acid.

Acknowledgments

GP and LP designed the study and collected data from recruited cases. SK analyzed data and performed the statistics. MM, NL, AT, GO, RI and TO analysed and wrote the Results and Discussion section including the literature review, prepared the manuscript, translated it and managed all the correspondence for publishing. All authors read and approved the final manuscript.

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