

Correlations of IL-6, IL-6R, IL-10 and IL-17 gene polymorphisms with the prevalence of COVID-2019 infection and its mortality rate

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Abstract

The pathogenesis of COVID-19 implicates a potent inflammatory response resulting in cytokine storm. We aimed to evaluate association between polymorphisms in *IL-6* gene at rs1800796/rs1800795, *IL-6R* at rs2228145, *IL-10* at rs1800896 and rs1800871, *IL-17* at rs2275913 and rs76378, and the prevalence (per million) and mortality rates (per million) of COVID-19 among populations of China, Japan, India, Iran, Spain, Italy, Mexico, Netherlands, Sweden, Turkey, Finland, Brazil, Czechia, Russia, Poland. AG and GG genotypes of rs2275913 in *IL-17A* was found to be correlated with prevalence and mortality rates, especially in Spain and Brazil populations ($p < 0.05$) while TT genotype of rs763780 in *IL-17F* was not dependent on the high frequencies in all populations. However, the polymorphisms in *IL-6*, *IL-6R* and *IL-10* appear not to be correlated with prevalence and mortality rates. The variations in the prevalence of COVID-19 and its mortality rates among countries may be explained by cytokine storm differed by the polymorphisms of rs2275913 locus in *IL-17A* gene. However, the prevalence of infection differs from severity of COVID-19, based on many factors such as public awareness, behaviors and antiviral policy of countries. Yet, the severity of disease induced by viral infection might be associated with genetic host factors including immune profiling.

Introduction

Since December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has given rise to emerging respiratory infections with a pandemics diffusion.¹ By 7th September 2020, the global number of confirmed cases of COVID-19 reached 27,066,438 with a mortality of 885,480² In Turkey, 279,806 cases and 6673 deaths have been confirmed until 7th September 2020.² Most patients present with mild symptoms that are not life-threatening, however, the mortality rates are in such considerable amount among large population base.²

The pathogenesis of COVID-19 implicates a potent inflammatory response, involving a complex group of mediators including interleukins.³⁻¹⁰ These pleiotropic cytokines are secreted at the region of inflammation and released into the circulation by a variety of different cell types, including macrophages, lymphocytes, endothelial cells, epithelial cells and fibroblasts during sepsis and acute organ injuries.¹⁰ There has recently found a number of studies reporting that the cytokine storms take part in the course of COVID-19.³⁻⁵ Principally, SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete pro-inflammatory cytokines, such as interleukin-6 (IL-6) and IL-17.^{6,7} IL-6 acts as a key pro-inflammatory mediator for the induction of the acute phase response,¹¹ resulting in a variety of local and systemic fluctuations including fever, leucocytes recruitment and activation and hemodynamic changes. Considering the key role of interleukins in mediating the acute phase response, they have been nominated as prognostic biomarkers in sepsis and various acute organ injuries in clinical and experimental studies. Some studies have also reported that patients with severe COVID-19 have higher levels of IL-2, IL-6, IL-7, IL-10 than patients with mild and moderate infections.^{4,8,9} In viral infections, IL-10 is highly abundant, especially during the adaptive immune response.¹² IL-17 was found to be increased in intensive-care COVID-19 patients compared to controls.⁴ Therefore, these key inflammatory factors in COVID-19 are of great interest in understanding the cytokine storm-related mortality in severe cases.³

The basis and value of single nucleotide polymorphisms (SNPs) relation to immune responses are called "immunogenetic profiling".¹³ SARS-CoV-2 infection is claimed to be correlated with IL-6 polymorphism. Recently, it was reported that *IL6* rs1800795 G allele could act as a protective factor while *IL10* rs1800896 A allele could act as a risk indicator in Pneumonia-induced sepsis in Chinese Han patients. In addition, these *IL6* polymorphisms were associated with clinical stage of sepsis and have crucial effects on the secretion of IL-6 and IL-10 in the patients.¹⁴ Therapies by IL6 receptor antagonists are proposed to be a therapeutic option for the therapy of cytokine storm syndrome in SARS-CoV-2 infected patients.¹⁵ Therefore, we hypothesized that single nucleotide polymorphisms (SNPs) in *IL-6*, *IL-6R*, *IL-10* and *IL-17* genes may participate in the clinical course of COVID-19 infection.

The main goal of this study was to evaluate if there is any association between the *IL-6* gene polymorphism at rs1800796/rs1800795 locus, *IL-6R* at rs2228145 locus, *IL-10* at rs1800896 and rs1800871 loci, *IL-17* at rs2275913 and rs76378 loci, and the prevalence of COVID-19 and the mortality rates among populations of 15 countries including Turkey.

Materials And Methods

To test this hypothesis and to limit confounding bias (latitude, etc.), we focused on the countries whose *IL-6* gene polymorphisms at rs1800796 and rs1800795 loci, *IL-6R* at rs2228145 locus, *IL-10* at rs1800896 and rs1800871 loci, *IL-17* at rs2275913 and rs76378 loci were defined and the allele frequencies were reported in 37 studies.¹⁶⁻⁵² We searched the literature for interleukin genes polymorphisms in China, Japan, India, Iran, Spain, Italy, Mexico, Netherlands, Sweden, Turkey, Finland, Brazil, Czechia, Russia, Poland. We recorded the total number of cases of COVID-19 and per million population in each of the countries to find the prevalence, and the mortality rates caused by the Coronavirus infection recorded at 7th September 2020 according to WHO COVID-19 Weekly Epidemiological Update .²

All data were analyzed by SPSS (statistical package for social sciences) for Windows 22 program. In the analysis of the data, first the assumptions that must be met were tested to decide which tests (parametric / nonparametric tests) to apply. Shapiro Wilk test, kurtosis and skewness values which are other assumptions of normal distribution, and histogram graph were used to decide the normality of the distribution. Considering the insufficient number of data in each group, it was decided that the data did not exhibit normal distribution. The relationship between independent variables was examined with Spearman correlation coefficient (rho). In the interpretation of whether the obtained values are significant or not, 0.05 significance level was used as a criterion.

Results

Population diversities of *IL-6* gene polymorphisms at rs1800796/rs1800795 loci showed that the populations of China, Spain, Sweden and Poland mostly have GC genotype while the populations of India, Mexico, Turkey, Brazil and Russia mostly have GG genotype. Japanese population mostly showed CC genotype for rs1800796 polymorphism (Table 1).

Population diversities of *IL-6R* gene polymorphisms at rs2228145 locus revealed that the populations of all countries except India and Sweden mostly have AC genotype while Indian and Swedish populations have AA genotype at rs2228145 locus. The prevalence of COVID-19 infection and relevant mortality rates per country recorded at 7th September 2020 showed that Spain and Brazil had the highest number of COVID-19 cases and mortality rates per million of the populations of countries involved in the study (Table 1).

Correlation between the frequencies of rs1800796/rs1800795 and rs2228145 polymorphisms, and the prevalence of COVID-19 and mortality rates per country demonstrated that there was no significant correlation between the prevalence (per million), mortality rates (per million), and these polymorphisms found in *IL-6* and *IL-6R* genes (Table 2).

Population diversities of *IL-10* gene polymorphisms at rs1800896 locus showed that the populations of China and Mexico mostly have AA genotype while the populations of India, Iran, Spain, Netherland, Finland, Brazil and Czechia mostly have AG genotype. Italian population mostly showed GG genotype for rs1800896 polymorphism (Table 3). Population diversities of *IL-10* gene polymorphisms at rs1800871 locus showed that the populations of Spain, Italy, Finland and Czechia mostly have CC genotype while the populations of India, Iran, Mexico, Netherland and Brazil mostly have CT genotype. Only Chinese population mostly showed TT genotype for rs1800871 polymorphism (Table 3).

Correlation between the frequencies of rs1800896 and rs1800871 polymorphisms, and the prevalence of COVID-19 and mortality rates per country demonstrated that there was no significant correlation between the prevalence (per million), mortality rates (per million), and these polymorphisms found in *IL-10* gene (Table 4).

Population diversities of *IL-17A* gene polymorphism at rs2275913 revealed that the populations of China, Japan, Iran, Finland and Czechia mostly have AG genotype while Spain, Mexico, Netherlands, Turkey and Brazil populations have GG genotype at rs2275913 locus (Table 5). Population diversities of *IL-17F* gene polymorphism at rs763780 locus revealed that all populations generally have TT genotype (Table 5).

Correlation analysis between the frequencies of rs2275913 polymorphism in *IL-17A* gene and prevalence of COVID-19 and mortality rates per country demonstrated that there was positive significant correlation between the prevalence (per million), mortality rates (per million), and GG genotype ($p < 0.05$) while there was negative correlation between those rates and AG genotype ($p < 0.05$). For AA genotype, a significant negative correlation was present between the prevalence and the frequency of rs2275913 polymorphism among countries (Table 6).

Correlation analysis between the frequencies of rs763780 polymorphism in *IL-17F* gene and prevalence of COVID-19 and mortality rates per country demonstrated that there was negative significant correlation between the prevalence (per million) and mortality rates (per million), and CC genotype ($p < 0.05$). However, no significant correlation was found between the prevalence (per million) and mortality rates (per million), and the frequencies TT and CC genotypes at rs763780 locus (Table 6).

Discussion

In the present study, AG and GG genotypes of rs2275913 locus in *IL-17A* gene were found to confer COVID-19 susceptibility to the populations of Spain and Brazil. TT genotype of rs763780 locus in *IL-17F* gene was not found to confer any susceptibility to any populations due to the high frequencies in all populations of selected countries (China, Japan, Iran, Spain, Mexico, Netherlands, Turkey, Finland, Brazil, Czechia). However, the polymorphisms in *IL-6*, *IL-6R* and *IL-10* genes appear not to be correlated with the prevalence (per million) of COVID-19 infection and mortality rates (per million) due to this infection. The variations in the prevalence of COVID-19 and its mortality rates among countries may be explained by cytokine storm differed by the polymorphisms of rs2275913 locus in *IL-17A* gene.

IL-6 is an important member of the cytokine network and plays a central role in acute inflammation and cytokine storm.⁵³ During the classical signal transduction of IL-6, IL-6 binds to its receptor IL-6R to form a complex and then binds to the transmembrane glycoprotein 130 to initiate intracellular signal transduction triggering biological functions such as proliferation, differentiation, oxidative stress, immune regulation, etc.⁵⁴ IL-6 can promote T-cell population expansion and activation and B-cell differentiation, regulate the acute phase response and release of a large number of cytokines. SARS-CoV-2 activates the innate and adaptive immune systems, resulting in the release of a large number of cytokines, including IL-6. This results in a systemic inflammatory response called cytokine release syndrome (CRS) in a large number of patients with severe COVID-19, which is an important reason of death.⁵⁵ On the other hand, polymorphisms in the IL6 was linked to certain viral infections like hepatitis C (HCV), influenza virus, and hepatitis B virus (HBV).⁵⁶ Mao et al. revealed that *IL6* rs1800795 G allele could act as a protective factor while *IL10* rs1800896 A allele could act as a risk indicator in pneumonia-induced sepsis in Chinese Han patients. Furthermore, these *IL6* polymorphisms were associated with clinical stage of sepsis and affected the secretion of IL-6 and IL-10.¹⁴ A very recent meta-analysis reported a relation between the *IL6* gene polymorphism and predisposition as well as disease severity of pneumonia, suggested the carrier status of *IL6* allele with higher IL-6 production and pneumonia severity.⁵⁷ However, in the present study, we could not find a significant correlation between the frequencies of rs1800796/rs1800795 and rs2228145 polymorphisms in *IL-6* and *IL-6R* genes, probably due to the variations among the genetic immune profiling of populations.

IL-10 is one of the complex group of mediators participating in the pathogenesis of COVID-19. In influenza infection, IL-10 is highly abundant, especially during the adaptive immune response.⁵⁸ Serum IL-10 levels with IL-6 were found to be significantly higher in critical COVID-19 patients, than in moderate and severe patients. The levels of IL-10 were also reported to be positively correlated with CRP amount, and IL-6 and IL-10 were found to be predictive of disease severity.⁵⁹ The first study for IL-10 polymorphism in SARS did not show any significant association of this SNP with SARS.⁶⁰ A case-control study for cytokine genotyped the SNP IL-10 also did not find a significant association between the genotype and allele frequencies of IL-10 polymorphisms among the SARS patients in terms the death and survival ratio.⁶¹ This result is consistent with our present finding showing no significant correlation between two polymorphisms of *IL-10* gene (rs1800896 and rs1800871 loci) and the prevalence of SARS-CoV-2 and mortality rates due to its infection. However, we cannot exclude the role of IL-10, IL-6 and IL-6R

as the susceptibility genes for COVID-19, since other SNPs in these genes may also be involved in gene expression regulation. Further association studies on other SNPs, which could alter the gene expression level are required to ascertain the relationship of IL-6, IL-6R and IL-10 in COVID-19 infection.

IL-17 is the most well-known and multifunctional cytokine of a cytokine family. Its predominant either based on the gene expression or the trigger of precipitation. These two phenomena seem to affect the dominant effect of its expression as a protective cytokine or lead to a damaging hyper-inflammatory state.⁶² IL-17 and other T helper 17 cell-related pro-inflammatory cytokines, such as IL-1, IL-6, IL-15, TNF and IFN γ were found to be positively correlate with the severity of MERS-CoV, SARS-CoV and SARS-CoV-2.^{63,64} A retrospective analysis of IL-17 gene polymorphisms in patients with acute respiratory distress syndrome (ARDS) revealed that patients with a polymorphism that resulted in attenuated IL-17 production had an increased 30-day survival, whereas a genetic polymorphism that resulted in producing more IL-17 correlated with decreased survival.⁶⁵ Mikacenic et al. measured circulating IL-17A in ARDS and showed that elevated circulating and alveolar levels of IL-17A are associated with increased percentage of alveolar neutrophils, alveolar permeability and organ dysfunction in ARDS.⁶⁶ However, there is no detailed information about the association between frequency of polymorphisms of *IL-17A* and *IL-17F* genes of COVID patients among the populations. This is the first study showing the positive significant correlation between the prevalence and mortality rates in COVID-19 and GG genotype of rs2275913 SNP in *IL-17A* gene, additionally, a negative correlation between those prevalence and mortality rates and AG genotype. AA genotype also gave a significant negative correlation with the prevalence of disease among countries. We found another negative significant correlation between the prevalence and mortality rates, and the frequencies of CC genotype for rs763780 SNP in *IL-17F* gene, suggesting that the genetic variations in *IL-17* gene may be linked to the distribution of COVID-19 infection among nations.

The pathology of COVID-19 involves a complex interaction between the SARS-CoV2 and the body immune system. Vitamin D plays a major role regulating the immune system, including immune responses to viral infection.⁶⁷ Vitamin D has been reported to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokines, which are frequently observed in COVID-19 cases.⁶⁸ Recently, we reported the genetic polymorphism especially in the gene of vitamin D binding protein is associated with the increased risk of COVID-19 infection and its mortality among populations with white race.⁶⁹ Therefore, the correlation of the variations in interleukin gene polymorphisms and the prevalence of COVID-19 with its mortality rate may depend on the modulatory effect of Vitamin D metabolism in individuals which is determined by the genetic background. However, the prevalence of SARS COV-2 infection differs from the severity of COVID-19, by association with many factors such as public awareness, behaviors and antiviral policy of each country except the host genetic factors. On the contrary, the severity of the disease induced by viral infection might be associated with the genetic host factors including immune profiling. More detailed and large sampled studies about the genetic variations in infected patients with different degrees of severity are needed to explain the underlying mechanism of cytokine storm in COVID-19 patients.

Declarations

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

LKB and NH conceptualized and designed the study collected data, interpreted data, conducted literature review, drafted the manuscript, supervised the analysis, critical revision of the manuscript for important intellectual content and took responsible for the article.

Competing interests

The authors declare no competing interests.

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Tables

Table 1. Population diversities of *IL-6* (rs1800796/rs1800795) and *IL-6R* (rs2228145) polymorphisms, the prevalence of COVID-19 and mortality rates per country recorded at 7th Sep 2020

	rs1800796/ rs1800795			rs2228145			Prevalence ¹		Mortality ¹		
Country	GG	GC	CC	AA	AC	CC	Total	per million	Total	per million	Reference
China	13.2	44.3	42.4	-	-	-	90551	61.6	4737	3.2	Zhang <i>et al.</i> 2017 ¹⁶
Japan	6.7	35.8	57.5	35.0	49.00	16.00	71856	568.1	1363	10.8	Sugimoto <i>et al.</i> 2015 ¹⁷ Miwa <i>et al.</i> 2016 ¹⁸
India	68.6	26.4	5.0	51.6	44.00	4.40	4204613	3046.8	71642	51.9	Sundaresh <i>et al.</i> 2019 ¹⁹
Spain	41.1	47.7	12.2	38.3	45.70	16.00	498989	10672.5	29418	629.2	Lopez-Mejas <i>et al.</i> 2013 ²⁰ Jiménez-Sousa <i>et al.</i> 2017 ²¹
Mexico	43.9	41.5	14.5	15.0	55.20	29.80	629409	4881.7	67326	522.2	Vargas-Alarcon <i>et al.</i> 2012 ²² Ponce de León-Suárez <i>et al.</i> 2018 ²³
Sweden	22.1	59.3	18.6	52.7	36.60	10.70	84985	8415.0	5835	577.8	Suijkerbuijk <i>et al.</i> 2019 ²⁴
Turkey	96.0	4.0	0.0	-	-	-	279806	3317.6	6673	79.1	Sarsu <i>et al.</i> 2015 ²⁵
Brazil	77.7	20.2	2.1	36.4	46.70	16.90	4123000	19396.9	126203	593.7	Vargas <i>et al.</i> 2013 ²⁸ Mattos <i>et al.</i> 2017 ²⁹
Russia	89.7	8.6	1.7	39.5	51.50	9.00	1030690	7062.7	17871	122.5	Topchieva <i>et al.</i> 2018 ²⁶ Mitrokhin <i>et al.</i> 2017 ²⁷
Poland	31.4	43.3	25.3	41.8	44.30	13.90	70824	1871.3	2120	56.0	Lulińska-Kuklik <i>et al.</i> 2019 ³⁰

¹ Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report

Table 2. Correlation between *IL-6* (rs1800796/rs1800795) and *IL-6R* (rs2228145) polymorphisms and prevalence of COVID-19 and mortality rates per country

Spearman's rho		GG	GC	CC	AA	AC	CC
Prevalence per million	r	0.47	-0.01	-0.57	-0.02	0.07	0.35
	p	0.16	0.96	0.08	0.95	0.86	0.38
Mortality per million	r	0.37	0.13	-0.45	-0.14	0.19	0.45
	p	0.29	0.70	0.18	0.73	0.65	0.25

Table 3. Population diversities of *IL-10* (rs1800896 and rs1800871) polymorphisms, the prevalence of COVID-19 and mortality rates per country recorded at 7th Sep 2020

Country	rs1800896			rs1800871			Prevalence ¹		Mortality ¹		Reference
	AA	AG	GG	CC	CT	TT	Total	per million	Total	per million	
China	83.9	15.2	1.0	11.6	39.4	49.0	90551	61.6	4737	3.2	Gao <i>et al.</i> 2017 ³¹
India	34.0	48.8	17.2	40.4	46.8	12.8	71856	568.1	1363	10.8	Singh <i>et al.</i> 2017 ³²
Iran	37.4	41.2	21.4	12.2	45.0	42.8	4204613	3046.8	71642	51.9	Mohammadi <i>et al.</i> 2018 ³³
Spain	29.6	55.6	14.8	63.7	28.8	7.4	498989	10672.5	29418	629.2	Lopez-Hernandez <i>et al.</i> 2014 ³⁴
Mexico	42.9	37.0	20.1	22.8	41.6	35.6	629409	4881.7	67326	522.2	Juárez-Cedillo <i>et al.</i> 2019 ³⁵
Netherlands	29.3	54.3	16.5	45.7	46.3	7.9	84985	8415.0	5835	577.8	Stappers <i>et al.</i> 2014 ³⁶
Italy	14.5	41.3	44.1	61.4	30.7	7.8	279806	3317.6	6673	79.1	Bagnoli <i>et al.</i> 2007 ³⁷
Finland	34.4	47.0	18.5	59.3	34.2	6.5	4123000	19396.9	126203	593.7	Holster <i>et al.</i> 2018 ³⁸
Brazil	40.8	44.3	14.9	38.4	47.5	14.1	1030690	7062.7	17871	122.5	Braz <i>et al.</i> 2019 ³⁹
Czechia	28.1	56.7	15.2	55.6	38.8	5.6	70824	1871.3	2120	56.0	Borilova Linhartova <i>et al.</i> 2018 ⁴⁰

¹ Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report

Table 4. Correlation between *IL-10* (rs1800896 and rs1800871) polymorphisms and the prevalence of COVID-19 and mortality rates per country

Spearman's rho		AA	AG	GG	CC	CT	TT
Prevalence per million	r	0.04	0.01	0.10	0.09	0.18	0.14
	p	0.91	0.99	0.78	0.80	0.63	0.70
Mortality per million	r	-0.16	0.09	0.13	0.42	-0.12	-0.10
	p	0.65	0.80	0.73	0.23	0.75	0.78

Table 5. Population diversities of *IL-17A* (rs2275913) and *IL-17F* (rs763780) polymorphisms, the prevalence of COVID-19 and mortality rates per country recorded at 7th Sep 2020

Country	rs2275913			rs763780			Prevalence ¹		Mortality ¹		Reference
	AA	AG	GG	TT	TC	CC	Total	per million	Total	per million	
China	21.5	45.6	32.9	79.5	19.3	1.2	90551	61.6	4737	3.2	Wang <i>et al.</i> 2015 ⁴¹
Japan	11.4	57.2	31.4	79.8	18.2	2.0	71856	568.1	1363	10.8	Kasamatsu <i>et al.</i> 2017 ⁴² Kawaguchi <i>et al.</i> 2006 ⁴³
Iran	15.1	43.0	41.9	88.4	11.0	0.6	4204613	3046.8	71642	51.9	Tayefinasrabadi <i>et al.</i> 2020 ⁴⁴
Spain	12.0	39.0	49.0	93.4	6.6	0.0	498989	10672.5	29418	629.2	Prieto-Pérez <i>et al.</i> 2015 ⁴⁵
Mexico	1.8	27.9	70.3	76.0	24.0	0.0	629409	4881.7	67326	522.2	Montúfar-Robles <i>et al.</i> 2018 ⁴⁶ Escamilla-Tilch <i>et al.</i> 2014 ⁴⁷
Netherlands	15.5	42.1	42.4	91.5	8.5	0.0	84985	8415.0	5835	577.8	Stappers <i>et al.</i> 2014 ³⁶
Turkey	18.1	30.1	51.8	90.4	9.6	0.0	279806	3317.6	6673	79.1	Akbulut <i>et al.</i> 2017 ⁴⁸ Pehlivan <i>et al.</i> 2020 ⁴⁹
Finland	19.1	44.7	36.0	-	-	-	4123000	19396.9	126203	593.7	Liehu-Martiskainen <i>et al.</i> 2017 ⁵⁰
Brazil	7.6	33.8	58.6	90.0	9.6	0.5	1030690	7062.7	17871	122.5	Rocha Loures <i>et al.</i> 2018 ⁵¹
Czechia	12.0	51.0	37.0	88.0	12.0	0.0	70824	1871.3	2120	56.0	Navratilova <i>et al.</i> 2012 ⁵²

¹ Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report

Table 6. Correlation between IL-17A (rs2275913) and IL-17F (rs763780) polymorphisms and the prevalence of COVID-19 and mortality rates per country

Spearman's rho		AA	AG	GG	TT	TC	CC
Prevalence per million	r	-0.67	-0.73	0.82	0.17	-0.14	-0.68
	p	0.03	0.02	0.01	0.67	0.72	0.04
Mortality per million	r	-0.4	-0.83	0.83	0.48	-0.45	-0.88
	p	0.26	0.01	0.01	0.19	0.22	0.01