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RESEARCH ARTICLE

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Correlation between interleukin gene polymorphisms and current prevalence and mortality rates due to novel coronavirus disease 2019 (COVID-2019) in 23 countries

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Abstract

Background: The novel coronavirus disease 2019 (COVID-19) infection may rely on a potential genetic background for the variations in the inflammatory response. We aimed to investigate the possible correlation between polymorphisms in *the IL-6* gene at rs1800796/rs1800795, in *IL-6R* at rs2228145, in *IL-10* at rs1800896 and rs1800871, in *IL-17* at rs2275913 and rs763780 loci, and COVID-19 prevalence and mortality rates among populations of 23 countries.

Methods: We searched the literature for polymorphisms in China, Japan, India, Spain, Mexico, Sweden, Turkey, Brazil, Russia, Poland, Italy, South Africa, Netherlands, Greece, Germany, UK, Iran, Finland, Czechia, Tunisia, Norway, Egypt, Croatia. We recorded the prevalence and mortality rates (per million) caused by the Coronavirus infection recorded on 7th September 2020 and 6th December 2020.

Results: There was a significant positive correlation between the frequency of AG genotype of rs1800896 and prevalence recorded on 6th December 2020 (r: 0.53, r^2: 0.28, $p < .05$). There was a significant negative correlation between the mortality rates recorded on 7th September, and the AG genotype of rs2275913 (r: −0.51, r^2: 0.26, $p < .05$). There was a significant positive correlation between the prevalence recorded on 6th December, and TT genotype at rs763780 (r: 0.65, r^2:0.42, $p < .05$) while a negative correlation between prevalence and TC genotype at rs763780 (r: −0.66, r^2: 0.43, $p < .05$). Also, a significant negative correlation was found between mortality rates recorded on 6th December 2020 and CC genotype at rs763780 (r: −0.56, r^2: 0.31, $p < .05$).

Conclusion: The variations in prevalence of COVID-19 and its mortality rates among countries may be explained by the polymorphisms at rs1800896 in *IL-10*, rs2275913 in *IL-17A*, and rs763780 loci in the *IL-17F* gene.

KEYWORDS
coronavirus disease 2019, correlation, interleukin, polymorphism

1 | INTRODUCTION

Beginning from December 2019, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has evolved into a pandemic and has given rise to challenging health concerns worldwide.[1] By 6th December 2020, the global number of confirmed cases of COVID-19 reached 65 872 391 with a total loss of life of 1 523 656.[2] In Turkey, 533 198 cases and 14 705 deaths have been confirmed up till 6th December 2020.[2] Although several measures have been taken globally and nationally to prevent the rapid transmission of infection, the pandemic outbreak cannot be decelerated due to several factors including the variations in the genetic background and host defense mechanisms among populations.[1]

The pathogenesis of COVID-19 harbors an effective inflammatory response, triggering a complex group of mediators including interleukins.[3] In the course of the disease, excessive production of pro-inflammatory cytokines results in a cytokine storm which is responsible for the severe progression of the disease and the acute organ injuries.[1] The underlying mechanism is that SARS-CoV-2 can rapidly activate pathogenic T helper cell type 1 (Th1) cells to secrete pro-inflammatory cytokines including interleukin-6 (IL-6), IL-10, and IL-17.[4] COVID-19 patients were reported to have high IL-6 and IL-10 levels and low $CD4^+$ T and $CD8^+$ T cell levels associated with the disease severity.[5] Some studies have also reported that the patients with severe COVID-19 have higher levels of IL-2, IL-6, IL-7, IL-10 than patients with mild and moderate infections.[3–5] IL-17 levels were found to be increased in COVID-19 patients hospitalized in the intensive-care unit compared to the control patients.[6] Therefore, these key inflammatory factors in COVID-19 have paramount importance in understanding the cytokine storm-related mortality in severe cases.[3]

Genetic polymorphisms implicated in understanding the basis of diseases also allow for the prevention of the spread of infections, and for the development of potentially effective treatments against the diseases. One common type of these polymorphisms, the single nucleotide polymorphisms (SNPs) are known to be effective in the pathways that play an important role in the attachment of the microbiological agent to the host cell, in the host's resistance to the diseases, in the susceptibility to disease and the severity of diseases.[1] There are growing numbers of reports stating that severe symptoms of COVID-19 might be attributed to the human genetic variants in genes related to immune deficiency, pneumonia, sepsis, and/or cytokine storm.[7] Recently, it was reported that the G allele of the rs1800795 locus in the *IL6* gene could act as a protective factor while the A allele of rs1800896 in *IL10* gene could act as a risk indicator in pneumonia-induced sepsis in Chinese Han patients. In addition, these polymorphisms in *IL6* gene were associated with the clinical stage of sepsis and have crucial effects on the secretion of IL-6 and IL-10 in the patients.[8] On the other hand, a report of IL-17 gene polymorphisms in patients with an acute respiratory distress syndrome (ARDS) revealed that 30-day survival rate increased in the patients with a genetic polymorphism that resulted in an attenuated IL-17 production, whereas a polymorphism that resulted in the production of more IL-17 correlated with the decreased survival rate.[9] Therefore, we hypothesized that SNPs in *IL-6*, *IL-6R*, *IL-10*, *IL-17A*, and *IL-17F* genes may participate in the clinical course of COVID-19 infection and the survival/mortality rates due to this infection.

The main goal of this study was to evaluate a possible correlation between the common polymorphisms at rs1800796/rs1800795 locus of *IL-6* gene, at rs2228145 locus of *IL-6R* gene, at rs1800896 and rs1800871 loci of *IL-10* gene, at rs2275913 locus of *IL-17A* gene and rs763780 locus of *IL-17F* gene, and the prevalence of COVID-19 and the mortality rates among populations of 23 countries including Turkey.

2 | MATERIALS AND METHODS

To test this hypothesis and to limit any confounding bias (latitude, etc.), we focused on the countries whose *IL-6* gene polymorphisms at rs1800796 and rs1800795 loci, *IL-6R* gene polymorphism at rs2228145 locus, *IL-10* gene polymorphism at rs1800896 and rs1800871 loci, *IL-17A* gene polymorphism at rs2275913 and *IL-17F* gene polymorphism at rs763780 loci were defined and the allele frequencies were reported in 54 studies.[10–63] We searched the literature for the interleukin gene polymorphisms determined in the populations of China, Japan, India, Spain, Mexico, Sweden, Turkey, Brazil, Russia, Poland, Italy, South Africa, Netherlands, Greece, Germany, UK, Iran, Finland, Czechia, Tunisia, Norway, Egypt, Croatia. We recorded the total number of cases of COVID-19 and the number of cases per million population in each of the countries to find the prevalence per million, and the mortality rates per million, caused by the Coronavirus infection recorded on 7th September 2020 and 6th December 2020 according to the WHO COVID-19 Weekly Epidemiological Update.[2] As this study includes the literature data, ethical approval is not required.

At first, the hypothesis that must be met were tested to decide which tests (parametric/nonparametric tests) are to be applied in the analysis of data. The normality of the distribution was tested by the Shapiro Wilk test, kurtosis and skewness values, and histogram graph. As the amount of data in each group was insufficient, the variables did not show a normal distribution. The Spearman correlation coefficient (rho) was used to evaluate the relationship between independent variables. The significance level was 0.05. For the analysis of all data, SPSS (statistical package for social sciences) for Windows 22 program was used.

3 | RESULTS

Population diversities of *IL-6* gene polymorphisms at rs1800796/rs1800795 loci showed that the populations of India, Mexico, Turkey, Brazil, Russia, Italy, South Africa, Netherland, Greece frequently have the GG genotype while the populations of China, Spain,

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 on 7th September and 6th December of 2020

Country	rs1800796/rs1800795			rs2228145			Prevalence[a]		Mortality[a]		Prevalence[b]		Mortality[b]		Reference
	GG	GC	CC	AA	AC	CC	Total	per million	Total	per million	Total	per million	Total	per million	
China	13.2	44.3	42.4	–	–	–	90551	61.6	4737	3.2	94160	64	4753	3.23	Zhang et al.[10]
Japan	6.7	35.8	57.5	35.0	49.0	16.0	71856	568.1	1363	10.8	160098	1265.83	2315	18.3	Sugimoto et al.,[11] Miwa et al.[12]
India	68.6	26.4	5.0	51.6	44.0	4.40	4204613	3046.8	71642	51.9	9644222	6988.54	140182	101.58	Sundaresh et al.[13]
Spain	41.1	47.7	12.2	38.3	45.7	16.0	498989	10672.5	29418	629.2	1684647	36031.55	46252	989.25	Lopez-Mejas et al.,[14] Jiménez-Sousa et al.[15]
Mexico	43.9	41.5	14.5	15.0	55.2	29.8	629409	4881.7	67326	522.2	1156770	8971.89	108863	844.34	Vargas-Alarcon et al.[16] Ponce de León-Suárez et al.[17]
Sweden	22.1	59.3	18.6	52.7	36.6	10.7	84985	8415.0	5835	577.8	278912	27617.06	7067	699.75	Suijkerbuijk et al.[18]
Turkey	96.0	4.0	0.0	–	–	–	279806	3317.6	6673	79.1	533198	6322.08	14705	174.36	Sarsu et al.[19]
Brazil	77.7	20.2	2.1	36.4	46.7	16.9	4123000	19396.9	126203	593.7	6533968	30739.49	175964	827.83	Vargas et al.,[20] Mattos et al.[21]
Russia	89.7	8.6	1.7	39.5	51	9.0	1030690	7062.7	17871	122.5	2460770	16862.16	43141	295.62	Topchieva et al.,[22] Mitrokhin et al.[23]
Poland	31.4	43.3	25.3	41.8	44.3	13.9	70824	1871.3	2120	56.0	1054273	27856.47	19861	524.78	Lulińska-Kuklik et al.[24]
Italy	80.3	18.4	0.013	36.0	45.0	19.0	276338	4570	35534	588	1709991	28282.16	59514	984.32	Ruberto and Santovito[25]
South Africa	72.0	26.0	2.0	54.0	34.0	13.0	636884	10738	14779	249	810449	13664.93	22067	372.07	Suijkerbuijk et al.[18]
Netherland	84.0	14.0	2.0	39.0	45.0	16.0	74715	4360.4	6234	363.82	549784	32085.68	9649	563.12	Heidema et al.[26]
Greece	63.3	30.0	6.67	–	–	–	11386	1092	280	27	114568	10991.79	2902	278.42	Plataki et al.[27]
Germany	30.0	48.0	22.0	50.0	0	50.0	249	2984	9325	111	1171322	13980.27	18772	224.05	Schotte et al.[28]
UK	38.0	44.0	18.0	32.5	25.8	41.7	344168	5070	41549	612	1705975	25129.99	61014	898.77	Fishman et al.[29]

[a]Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report.

[b]Recorded on 6th Dec 2020 from WHO Coronavirus disease (COVID-19) Situation Report.

Sweden, Poland, Germany, and the UK frequently have GC genotype. Only the Japanese population frequently showed the CC genotype for rs1800796 polymorphism (Table 1). Population diversities of *IL-6R* gene polymorphisms at rs2228145 locus revealed that the populations of Japan, Spain, Mexico, Brazil, Russia, Poland, Italy, Netherland frequently have the AC genotype while Indian, Swedish and South African populations have AA genotype at rs2228145 locus. There was no heterozygosity for *the IL-6R* gene at the rs2228145 locus while only the UK population showed the highest frequency of CC genotype (Table 1).

The prevalence of COVID-19 infection and relevant mortality rates per country recorded on 7th September showed that Brazil and South Africa had the highest number of COVID-19 cases while Spain and the Netherlands reached the highest number on 6th December 2020. Spain and UK showed the highest mortality rates per million of the populations on 7th September while Spain and Italy showed the highest rates on 6th December 2020 among 16 countries involved in the study (Table 1).

The analysis between the frequencies of rs1800796/rs1800795 polymorphism in *IL-6* gene and rs2228145 polymorphism in *IL-6R* gene, 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 the frequencies of polymorphisms found in *IL-6* and *IL-6R* genes ($p > .05$) (Table 2).

Population diversities of *IL-10* gene polymorphisms at rs1800896 locus showed that the populations of China, Mexico, Tunisia, and Japan frequently have the AA genotype while the populations of India, Iran, Spain, Netherland, Finland, Brazil, Czechia, Poland, Germany, Norway, and the UK frequently have the AG genotype. The frequency of GG genotype of rs1800896 polymorphism was the highest only among the Italian population (-Table 3). Population diversities of *IL-10* gene polymorphisms at rs1800871 locus showed that the populations of Spain, Italy, Finland, Czechia, Japan, Norway, and the UK frequently have CC genotype while the populations of India, Iran, Mexico, Netherland, Brazil, and Tunisia frequently have CT genotype. Only Chinese and German populations frequently showed TT genotype for rs1800871 polymorphism (Table 3).

The analysis between the frequencies of rs1800896 and rs1800871 polymorphisms of *IL-10* gene, and the prevalence of COVID-19 and mortality rates recorded on 7th September and 6th December 2020 per country demonstrated that there was no significant correlation between the prevalence (per million), mortality rates (per million), and the frequencies of these polymorphisms found in *IL-10* gene except the frequency of AG genotype at rs1800896 locus (Table 4). There was a statistically significant positive correlation between the frequency of AG genotype and the prevalence of COVID-19 cases recorded on 6th December 2020 (r: 0.53, r^2: 0.28, $p < .05$). 28% of the variability among the number of cases may be explained by the frequency of AG genotype at rs1800896 among populations (Figure S1).

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

The 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 a significant negative correlation between the mortality rates (per million) recorded on 7th September 2020, and AG genotype (r: −0.51, r^2:0.26, $p < .05$) while there was no significant correlation between the prevalence and mortality rates recorded on 6th December 2020 and any genotype of the rs2275913 polymorphism (Table 6). 26% of the variability among the mortality rates may be explained by the frequency of AG genotype at rs2275913 among the populations (Figure S2).

The analysis between the frequencies of rs763780 polymorphism in *IL-17F* gene and the prevalence of COVID-19 cases and mortality rates per country demonstrated that there was a significant positive correlation between the prevalence (per million) recorded on 6th December 2020, and TT genotype (r: 0.65, r^2: 0.42, $p < .05$) while a negative correlation was found between that prevalence and TC genotype (r: −0.66, r^2: 0.43, $p < .05$). 42% and 43% of the variability among the number of cases may be explained by the frequency of TT and TC genotypes at rs763780, respectively (Figure S3). Also, a significant negative correlation was found between the mortality rates (per million) recorded on 6th December

TABLE 2 Correlation between *IL-6* (rs1800796/rs1800795) and *IL-6R* (rs2228145) polymorphisms and prevalence of COVID-19 and mortality rates for all countries

Date	SNP		Prevalence per million		Mortality per million	
			r	*p*	*r*	*p*
7th September 2020	rs1800796/ rs1800795	GG	0.40	.13	0.25	.35
		GC	−0.13	.64	0.06	.82
		CC	−0.47	.07	−0.32	.23
	rs2228145	AA	0.21	.46	−0.18	.54
		AC	−0.08	.79	−0.13	.65
		CC	−0.05	.88	0.40	.15
6th December 2020	rs1800796/ rs1800795	GG	0.25	.34	0.19	.47
		GC	0.01	.97	0.09	.73
		CC	−0.25	.34	−0.24	.37
	rs2228145	AA	0.10	.73	−0.26	.37
		AC	−0.14	.63	−0.05	.86
		CC	0.18	.53	0.43	.13

r: Spearman's rho.

TABLE 3 Population diversities of *IL-10* (rs1800896 and rs1800871) polymorphisms, the prevalence of COVID-19 and mortality rates per country recorded on 7th September and 6th December of 2020

Country	rs1800896			rs1800871			Prevalence[a]		Mortality[a]		Prevalence[b]		Mortality[b]		Reference
	AA	AG	GG	CC	CT	TT	Total	per million	Total	per million	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	94160	64	4753	3.23	Gao et al.[30]
India	34.0	48.8	17.2	40.4	46.8	12.8	71856	568.1	1363	10.8	9644222	6988.54	140182	101.58	Singh et al.[31]
Iran	37.4	41.2	21.4	12.2	45.0	42.8	4204613	3046.8	71642	51.9	1028986	12250.85	50016	595.48	Mohammadi et al.[32]
Spain	29.6	55.6	14.8	63.7	28.8	7.4	498989	10672.5	29418	629.2	1684647	36031.55	46252	989.25	Lopez-Hernandez et al.[33]
Mexico	42.9	37.0	20.1	22.8	41.6	35.6	629409	4881.7	67326	522.2	4881.68	67326	522.18	1156770	Vargas-Alarcon et al.[16]
Netherlands	29.3	54.3	16.5	45.7	46.3	7.9	84985	8415.0	5835	577.8	549784	32085.68	9649	563.12	Stappers et al.[34]
Italy	0.02	20.0	78.0	61.4	30.7	7.8	279806	3317.6	6673	79.1	1709991	28282.16	59514	984.32	Ruberto and Santovito,[25] Bagnoli et al.[35]
Finland	34.4	47.0	18.5	59.3	34.2	6.5	4123000	19396.9	126203	593.7	27218	4912.36	415	74.9	Holster et al.[36]
Brazil	40.8	44.3	14.9	38.4	47.5	14.1	1030690	7062.7	17871	122.5	6533968	30739.49	175964	827.83	Braz et al.[37]
Czechia	28.1	56.7	15.2	55.6	38.8	5.6	70824	1871.3	2120	56.0	544179	50815.2	8815	823.14	Borilova Linhartova et al.[38]
Tunisia	40.5	39.7	19.8	44.4	52.3	3.2	4776	404	93	8	102991	8714.3	3526	298.34	Zidi et al.[39]
Japan	87.3	12.7	0	52.8	37.5	9.7	71419	565	1357	11	160098	1265.83	2315	18.3	Matsushita et al.[40]
Poland	22.8	51.3	25.9	45.92	39.29	14.79	70387	1860	2113	56	1054273	27856.47	19861	524.78	Mirowska et al.[41]
Germany	28.1	49.8	22.1	5.3	37.8	56.9	249	2984	9325	111	1171322	13980.27	18772	224.05	Gao et al.[42]
Norway	24.1	49.5	26.4	55.2	41.4	3.4	11120	2051	264	49	37371	6893.44	354	65.3	Myhr et al.[43]
UK	32.0	41.0	27.0	56.0	37.0	7.0	344168	5070	41549	612	1705975	25129.99	61014	898.77	Wallace et al.[44]

[a]Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report.

[b]Recorded on 6th Dec 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 in all countries

Date	SNP		Prevalence per million		Mortality per million	
			r	*p*	*r*	*p*
7th September 2020	rs1800896	AA	−0.13	.64	−0.13	.64
		AG	0.24	.37	0.24	.37
		GG	0.09	.74	0.09	.74
	rs1800871	CC	0.11	.68	0.11	.68
		CT	−0.03	.91	−0.03	.91
		TT	0.13	.63	0.13	.63
6th December 2020	rs1800896	AA	−0.33	.22	−0.21	.43
		AG	0.53	**.04**	0.21	.42
		GG	−0.03	.91	0.11	.68
	rs1800871	CC	0.17	.53	0.26	.33
		CT	0.06	.84	−0.06	.83
		TT	−0.02	.95	−0.04	.88

r: Spearman's rho.

2020 and CC genotype (*r*: −0.56, r^2: 0.31, $p < .05$; Table 6). Therefore, 31% of the variability among the mortality rates may be explained by the frequency of CC genotypes at rs763780 locus among populations (Figure S4).

4 | DISCUSSION

In the present study, the AG genotype of rs1800896 locus in *IL-10* gene, TT and TC genotypes of rs763780 locus in *IL-17F* gene were found to be correlated with the prevalence (per million) of COVID-19 infection while the AG genotype of rs2275913 was correlated with the mortality rates (per million) due to COVID-19 among all populations from the selected countries (China, India, Iran, Spain, Mexico, Netherlands, Italy, Finland, Brazil, Czechia, Tunisia, Japan, Poland, Germany, Norway, UK, Turkey, Egypt, and Croatia), especially those of Brazil, Spain, and the Netherlands, which have the highest prevalence and those of Spain, UK, and Italy, which have the highest mortality rates among 23 countries. However, the polymorphisms in the given loci of *IL-6* and *IL-6R* genes appear not to be correlated with the prevalence of COVID-19 infection and mortality rates. Although the frequencies of *IL-10* and *IL-17* gene polymorphisms may not directly correlate with the course and severity of COVID-19 infection, the present correlation analysis may be interpreted as that the IL-10 and IL-17 allele carrier status is associated with the variations in the prevalence and mortality rates due to COVID-19 infection among the populations. This analysis strengthens the notion that the polymorphisms in interleukin genes play pivotal roles in the worldwide unrestrainable spread of disease despite a number of serious national and international measures.

SARS-CoV-2 activates the innate and adaptive immune systems, leading to the release of several cytokines, including IL-6. This gives rise to a systemic inflammatory response called cytokine release syndrome (CRS) in lots of patients diagnosed with severe COVID-19, which accounts for the high mortality rates.[64] In addition, the polymorphisms in the *IL-6* gene were associated with specific viral infections including influenza virus, hepatitis C (HCV), and hepatitis B virus (HBV).[65] A very recent meta-analysis reported an association between a polymorphism in *the IL-6* gene and predisposition and disease severity of pneumonia, suggested that the *IL-6* allele carries a status of higher IL-6 production and pneumonia severity.[66] However, there was no study reporting the association between the frequency of *IL-6* and *IL-6R* gene variants and the prevalence and mortality rates of COVID-19 infection. The present study found no significant correlation between the frequencies of rs1800796/rs1800795 and rs2228145 polymorphisms in *IL-6* and *IL-6R* genes, respectively, probably due to the variations among the genetic background of immune profiling of populations. Therefore, we cannot exclude the role of *IL-6* and *IL-6R* as the susceptible genes for COVID-19 infection, as 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 the expression of *IL-6* and *IL-6R* genes in COVID-19 infection.

High levels of IL-10 were recorded in severe COVID-19 patients and found to be associated with the compensatory anti-inflammatory response syndrome that may be responsible for a greater number of secondary infections (50%) and sepsis (100%) reported in survivors.[67] The first study for *IL-10* polymorphism in SARS did not show any significant association of this SNP with SARS.[68] A case-control study for cytokine genotyped the SNP in *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 of the death and survival ratio.[69] This result is not consistent with our present finding showing a significant positive correlation between the frequency of AG genotype of rs1800896 and the prevalence of COVID-19 recorded on 6th December 2020. 28% of these variations in the number of cases among 23 populations selected for the study may be explained by the frequency of AG genotype of *the IL-10* gene variant.

IL-17 was found to be positively correlated with the severity of MERS-CoV, SARS-CoV, and SARS-CoV-2.[70] A retrospective analysis of *IL-17* gene polymorphisms in patients with 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.[71] Mikacenic et al.[72] measured circulating IL-17A in ARDS and showed that elevated circulating and alveolar levels of IL-17A are associated with an increased percentage of alveolar neutrophils, alveolar permeability, and organ dysfunction in ARDS. In another study, Ren et al.[73] found a potential association between polymorphisms in the *IL-17* gene (rs2275913 and

TABLE 5 Population diversities of *IL-17A* (rs2275913) and *IL-17F* (rs763780) polymorphisms, the prevalence of COVID-19, and mortality rates per country recorded on 7th September and 6th December of 2020

Country	rs2275913			rs763780			Prevalence[a]		Mortality[a]		Prevalence[b]		Mortality[b]		Reference
	AA	AG	GG	TT	TC	CC	Total	per million	Total	per million	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	94160	64	4753	3.23	Wang et al.[45]
Japan	11.4	57.2	31.4	79.8	18.2	2.0	71856	568.1	1363	10.8	160098	1265.83	2315	18.3	Kasamatsu et al.,[46] Kawaguchi et al.[47]
Iran	15.1	43.0	41.9	88.4	11.0	0.6	4204613	3046.8	71642	51.9	1028986	12250.85	50016	595.48	Tayefinasrabadi et al.[48]
Spain	12.0	39.0	49.0	93.4	6.6	0.0	498989	10672.5	29418	629.2	1684647	36031.55	46252	989.25	Prieto-Pérez et al.[49]
Mexico	1.8	27.9	70.3	76.0	24.0	0.0	629409	4881.7	67326	522.2	1156770	8971.89	108863	844.34	Montúfar-Robles et al.,[50] Escamilla-Tilch et al.[51]
Netherlands	15.5	42.1	42.4	91.5	8.5	0.0	84985	8415.0	5835	577.8	549784	32085.68	9649	563.12	Stappers et al.[34]
Turkey	18.1	30.1	51.8	90.4	9.6	0.0	279806	3317.6	6673	79.1	533198	6322.08	14705	174.36	Akbulut et al.,[52] Pehlivan et al.[53]
Finland	19.1	44.7	36.0	–	–	–	4123000	19396.9	126203	593.7	27218	4912.36	415	74.9	Liehu-Martiskainen et al.[54]
Brazil	7.6	33.8	58.6	90.0	9.6	0.5	1030690	7062.7	17871	122.5	6533968	30739.49	175964	827.83	Rocha Loures et al.[55]
Czechia	12.0	51.0	37.0	88.0	12.0	0.0	70824	1871.3	2120	56.0	544179	50815.2	8815	823.14	Navratilova et al.[56]
India	7.9	54.8	37.3	85.7	12.7	1.6	4113811	2981	70626	51	9644222	6988.54	140182	101.58	Poomarimuthu et al.[57]
Germany	12.7	43.4	43.9	–	–	–	249	2984	9325	111	1171322	13980.27	18772	224.05	Schieck et al.[58]
Norway	13.5	50.1	36.4	–	–	–	11120	2051	264	49	37371	6893.44	354	65.3	Nordang et al.[59]
Tunisia	3.5	32.2	64.3	15	85	0	4776	404	93	8	102991	8714.3	3526	298.34	Maalmi et al.[60]
Poland	16	53.6	30.4	91.2	8.8	0	70824	1871.34	2120	56.02	1054273	27856.47	19861	524.78	Wróbel et al.[61]
Egypt	5.8	39.8	54.4	76.4	23.2	0.4	99712	974	5511	54	118014	1153.22	6750	65.96	Hammad et al.[62]
Croatia	11	42.3	46.7	93.4	6.4	0.2	11739	2859	197	48	147454	35918.25	2102	512.03	Vrgoc et al.[63]

[a]Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report.

[b]Recorded on 6th Dec 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

Date	SNP		Prevalence per million		Mortality per million	
			r	*p*	*r*	*p*
7th September 2020	rs2275913	AA	−0.16	.55	−0.03	.90
		AG	−0.47	.06	−0.51	**.04**
		GG	0.48	.06	0.43	.09
	rs763780	TT	0.48	.08	0.47	.09
		TC	−0.48	.09	−0.46	.10
		CC	−0.23	.43	−0.34	.23
6th December 2020	rs2275913	AA	−0.16	.54	−0.30	.24
		AG	−0.14	.59	−0.47	.06
		GG	0.20	.43	0.48	.06
	rs763780	TT	0.65	**.01**	0.38	.18
		TC	−0.66	**.01**	−0.38	.18
		CC	−0.52	.06	−0.56	**.04**

rs763780) and susceptibility to hepatitis B virus (HBV) infection in the Han Chinese population. They showed that possession of the GG genotype and the G allele at rs2275913, and the TT genotype and the T allele at rs763780 might increase the risk of HBV infection.[73] However, there is no detailed information about the association between the allele frequencies of *IL-17A* and *IL-17F* genes, and the prevalence and mortality rates of COVID-19 patients among the populations. The present study found a significant negative correlation between the mortality rates recorded on 7th September and AG genotype of rs2275913 in *the IL-17A* gene. 26% of the variability in the mortality rates among populations may be explained by the frequency of AG genotype of *IL-17A* gene. A significant positive correlation between the prevalence recorded on 6th December and the frequency of TT genotype at rs763780, as well as a negative correlation between the prevalence and the frequency of TC genotype at rs763780 suggested that 42% and 43% of the variability in the prevalence of COVID-19 cases among the populations may be explained by the frequencies of TT and TC genotypes in *IL-17F*, respectively. Also, a significant negative correlation between the mortality rates recorded on 6th December 2020 and the frequency of CC genotype at rs763780 suggested that 31% of the variability in those rates among the populations may be explained by the frequency of CC genotype in *IL-17F* gene. In short, the genetic variations in *the IL-17* gene may be relatively linked to the distribution of COVID-19 infection among nations.

Of note, it is not easy to clarify the underlying reasons for variations in genetic information which lead to differences in the prevalence and mortality rates of COVID-19 infections due to lack of information about this novel virus. In addition, the differences in the source of control subjects, the study design, the patient ethnicities even in the same country, and the sample size may result in the discrepancies observed between studies. Still, there is a growing body of evidence suggesting that interleukins contribute to the effective antiviral immune responses, as well as promote and exacerbate virus-induced illnesses. For instance, several viruses may activate multiple IL-17-producing cell subsets that differ in several key biological activities.[74] Th17 cells, the major cell type producing IL-17, are very permissive to HIV infection and can promote the intracellular replication of HIV, such that the presence of these cells correlates well with HIV pathology.[75] Similarly, following an influenza infection of the lung, the presence of Th17 cells exacerbates pathology, while the number of Tc17 cells, a unique subset of $CD8^+$ T cells that can protect against the lethal influenza disease, is negatively associated with the morbidity and mortality.[76] Therefore, the diverse functions of IL-17 in viral infections may be attributed to the unique effector functions of different IL-17-producing cell subsets and the genetic variations in *IL-17* transcripts. However, it is essential to elucidate the association between interleukin gene polymorphisms and the risk of COVID-19 infection in each population. In this context, our study may provide an inside into this association, suggesting that the host genetic background may give a clue about the reason of high prevalence and mortality rates of COVID-19 infection among the populations.

The limitations of the present study include the assumption that the interleukin polymorphisms in the sampled subjects have followed the same frequencies with all populations in the previous studies, as well as the lack of all frequencies of three alleles of three interleukin genes for all countries. In addition, we could not give the difference between the mean cytokine levels of the healthy controls and of COVID-19 patients, and its correlation with the number of cases and mortality rates. In other words, we do not have the data to suggest that the expression levels of *IL-10* and *IL-17* genes are directly correlated with the COVID-19 infections or we could not conclude that the expression levels of *IL-6* and *IL-6R* genes are not correlated with the COVID-19 infections. Investigating the available data, we illustrated minor evidence for a possible association between *IL-10* and *IL-17* gene polymorphisms and the distribution of COVID-19 infection among nations. In addition, the difference in the age range, ethnicity, gender, comorbidities, and the size of the sample chosen from the population may affect the reported frequencies in different studies. We reduced some of these impacts by analyzing data from more recent studies which have collected a large number of samples, however, even the region where the healthy subjects collected may affect the estimation of frequency in different studies. These limitations can be addressed by following the mean interleukin levels and the frequencies of gene alleles among COVID-19 patients within a given population comparing with the healthy subjects, which is now unavailable in the literature. Another limiting factor is that the date of COVID-19 cases and mortality data presented by WHO was recorded for only two specific dates and these data are currently changing each day for each country. Despite all these limitations, the correlation between the genetic variations in the interleukin genes and the prevalence and mortality rates of COVID-19 cases in nations presented in this study may provide motivation for future investigations.

5 | CONCLUSION

In short, the correlation between the variations in interleukin gene polymorphisms and the prevalence of COVID-19 with its mortality rate may depend on the genetic background including the host defense system and immune profiling of the individuals. Apart from these host genetic factors, however, the prevalence of SARS COV-2 infection in each population does not stand for the severity of COVID-19, due to several factors such as the community knowledge, behaviors, and antiviral policy of each country. 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 different immune responses including the cytokine storm in COVID-19 patients.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly to the work.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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