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

Lutfiye Karcioglu Batur PhD | Nezih Hekim PhD

Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Biruni University, Istanbul, Turkey

Correspondence
Dr. Lutfiye Karcioglu Batur, Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Biruni University, Istanbul, Turkey.
Email: lbatur@biruni.edu.tr

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
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. 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. In Turkey, 533 198 cases and 14 705 deaths have been confirmed up till 6th December 2020. 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.

The pathogenesis of COVID-19 harbors an effective inflammatory response, triggering a complex group of mediators including interleukins. 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. 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. 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. 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. IL-17 levels were found to be increased in COVID-19 patients hospitalized in the intensive-care unit compared to the control patients. Therefore, these key inflammatory factors in COVID-19 have paramount importance in understanding the cytokine storm-related mortality in severe cases.

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. 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. 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. 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. 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.

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. 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. 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.

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 (GG) | rs1800796 (GC) | rs1800796 (CC) | rs2228145 (AA) | rs2228145 (AC) | rs2228145 (CC) | Prevalence$^a$ | Mortality$^a$ | Prevalence$^b$ | Mortality$^b$ | Reference                  |
|-------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------|---------------|---------------|---------------|---------------------------|
| China       | 13.2           | 44.3           | 42.4           | -              | -              |                | 90551         | 61.6          | 4737          | 32            | 94160/64                  | 4753/32.3                 | Zhang et al.10            |
| Japan       | 6.7            | 35.8           | 57.5           | 35.0           | 49.0           | 16.0           | 71856         | 568.1         | 1363          | 108          | 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               | Suijkerbijn 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  | 179564/827.83             | Vargas et al.,20 Mattos et al.21 |
| Russia      | 89.7           | 8.6            | 1.7            | 39.5           | 51.0           | 9.0            | 1030690       | 7062.7        | 17871         | 1225          | 2460770/16862.16  | 433141/295.62             | 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          | 560           | 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 Santovito25 |
| South Africa| 72.0           | 26.0           | 2.0            | 54.0           | 34.0           | 13.0           | 636884        | 10738         | 14779         | 249           | 810449/13664.93   | 22067/372.07              | Suijkerbijn et al.18      |
| Netherland  | 84.0           | 14.0           | 2.0            | 39.0           | 45.0           | 16.0           | 74715         | 4360.4        | 6234         | 36382         | 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, 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, r²: 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, r²: 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, r²: 0.42, p < .05) while a negative correlation was found between that prevalence and TC genotype (r = −0.66, r²: 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 | 0.13 | 0.25 | 0.35 |
| | | GC | −0.13 | 0.64 | 0.06 | 0.82 |
| | | CC | −0.47 | 0.07 | −0.32 | 0.23 |
| | rs2228145 | AA | 0.21 | 0.46 | −0.18 | 0.54 |
| | | AC | −0.08 | 0.79 | −0.13 | 0.65 |
| | | CC | −0.05 | 0.88 | 0.40 | 0.15 |
| 6th December 2020 | rs1800796/ rs1800795 | GG | 0.25 | 0.34 | 0.19 | 0.47 |
| | | GC | 0.01 | 0.97 | 0.09 | 0.73 |
| | | CC | −0.25 | 0.34 | −0.24 | 0.37 |
| | rs2228145 | AA | 0.10 | 0.73 | −0.26 | 0.37 |
| | | AC | −0.14 | 0.63 | −0.05 | 0.86 |
| | | CC | 0.18 | 0.53 | 0.43 | 0.13 |

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<sup>a</sup> Total per million | Mortality<sup>a</sup> Total per million | Prevalence<sup>b</sup> Total | Mortality<sup>b</sup> Total per million | Reference |
|---------|-----------|-----------|------------------------------------------|----------------------------------------|---------------------------|----------------------------------------|-----------|
|         | AA        | AG        | GG                                       |                                        | CC           | CT          | TT          |                                        |           |
| China   | 83.9      | 15.2      | 1.0                                      | 11.6                                   | 90551        | 61.6        | 4737        | 94160        | 64          | 4753        | 3.23       | Gao et al. 30 |
| India   | 34.0      | 48.8      | 17.2                                    | 40.4                                   | 71856        | 568.1       | 1363        | 9644222      | 6988.54     | 140182      | 101.58     | Singh et al. 31 |
| Iran    | 37.4      | 41.2      | 12.2                                    | 45.0                                   | 4204613      | 3046.8      | 71642       | 1028986      | 12250.85    | 50016       | 595.48     | Mohammadi et al. 32 |
| Spain   | 29.6      | 55.6      | 14.8                                    | 637                                    | 4988989      | 10672.5     | 29418       | 1684647      | 36031355    | 46252       | 989.25     | Lopez-Hernandez et al. 33 |
| Mexico  | 42.9      | 37.0      | 20.1                                    | 22.8                                   | 629409       | 4881.7      | 67326       | 4881.68      | 67326        | 522.18      | 1156770    | Vargas-Alarcon et al. 16 |
| Netherlands | 29.3  | 54.3      | 16.5                                    | 45.7                                   | 84985        | 8415.0      | 5835        | 549784       | 3208568     | 9649        | 563.12     | Stappers et al. 34 |
| Italy   | 0.02      | 200.0     | 78.0                                    | 614                                    | 278906       | 3317.6      | 6673        | 1709991      | 2828216     | 59514       | 984.32     | Ruberto and Santovito 25, Bagnoli et al. 35 |
| Finland | 34.4      | 470.0     | 18.5                                    | 593.6                                  | 4123000      | 19396.9     | 126203      | 27218        | 491236      | 415        | 74.9       | Holster et al. 36 |
| Brazil  | 40.8      | 443.0     | 14.9                                    | 38.4                                   | 1030690      | 7062.7      | 17871       | 6533968      | 3073949     | 175964      | 827.83     | Braz et al. 37 |
| Czechia | 28.1      | 567.0     | 15.2                                    | 55.6                                   | 70824        | 1871.3      | 2120        | 544179       | 508152      | 8815        | 823.14     | Borilova Linhartova et al. 38 |
| Tunisia | 40.5      | 397.0     | 19.8                                    | 444                                    | 4776         | 404         | 93          | 102991       | 87143       | 3526        | 298.34     | Zidi et al. 39 |
| Japan   | 87.3      | 127.0     | 0                                       | 528                                    | 71419        | 565         | 1357        | 160098       | 126583      | 2315        | 18.3       | Matsushita et al. 40 |
| Poland  | 22.8      | 513.0     | 25.9                                    | 45.92                                  | 70387        | 1860        | 2113        | 1054273      | 2785647     | 19861       | 524.78     | Mirowska et al. 31 |
| Germany | 28.1      | 498.0     | 22.1                                    | 53                                      | 249          | 2984        | 9325        | 1171322      | 1398027     | 18772       | 224.05     | Gao et al. 42 |
| Norway  | 24.1      | 495.0     | 26.4                                    | 55.2                                    | 11120        | 2051        | 264         | 37371        | 689344      | 354         | 65.3       | Myhr et al. 43 |
| UK      | 32.0      | 410.0     | 27.0                                    | 560                                    | 344168       | 5070        | 41549       | 1705975      | 2512999     | 61014       | 898.77     | Wallace et al. 44 |

<sup>a</sup>Recorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report.

<sup>b</sup>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. 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). 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. 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. The first study for IL-10 polymorphism in SARS did not show any significant association of this SNP with SARS. 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. 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. 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. Mikacenic et al. 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. 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 |
|---------------|-----------|----------|--------------|-------------|--------------|-------------|
|               | AA        | AG       | GC           | TT          | TC           | CC          |
|               | 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      | 323      |             |             |               |             |
| Japan         | 11.4      | 57.2     | 31.4        | 79.8        | 18.2         | 2.0         |
|               | 71856     | 568.1    | 1363        | 10.8        | 160098       | 1265.8      |
|               | 2315      | 18.3     |             |             |               |             |
| Iran          | 15.1      | 43.0     | 41.9        | 88.4        | 11.0         | 0.6         |
|               | 4204613   | 3046.8   | 71642       | 51.9        | 1028986      | 12250.8     |
|               | 50016     | 595.4    |             |             |               |             |
| 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   |             |             |               |             |
| 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   |             |             |               |             |
| 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   |             |             |               |             |
| 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   |             |             |               |             |
| Finland       | 19.1      | 44.7     | 36.0        | 90.6        | 9.6          | 0.5         |
|               | 4123000   | 19396.9  | 126203      | 593.7       | 27218        | 4912.36     |
|               | 415       | 749      |             |             |               |             |
| Brazil        | 7.6       | 33.8     | 58.6        | 90.0        | 9.6          | 0.5         |
|               | 1030690   | 7062.7   | 17871       | 122.5       | 6533968      | 30739.49    |
|               | 175964    | 82783    |             |             |               |             |
| Czechia       | 12.0      | 51.0     | 37.0        | 88.0        | 120.0        | 0.0         |
|               | 70824     | 1871.3   | 2120        | 56.0        | 544179       | 50815.2     |
|               | 8815      | 82314    |             |             |               |             |
| India         | 7.9       | 54.8     | 37.3        | 85.7        | 12.7         | 1.6         |
|               | 4113811   | 2981     | 70626       | 51          | 9644222      | 6988.54     |
|               | 140182    | 101.58   |             |             |               |             |
| Germany       | 12.7      | 43.4     | 43.9        | -           | -            | -           |
|               | 249       | 2984     | 9325        | 111         | 1171322      | 13980.27    |
|               | 18772     | 22405    |             |             |               |             |
| Norway        | 13.5      | 50.1     | 36.4        | -           | -            | -           |
|               | 11120     | 2051     | 264         | 49          | 37371        | 6893.44     |
|               | 354       | 65.3     |             |             |               |             |
| Tunisia       | 3.5       | 32.2     | 64.3        | 15          | 85           | 0           |
|               | 4776      | 404      | 93          | 8           | 102991       | 8714.3      |
|               | 3526      | 298.34   |             |             |               |             |
| Poland        | 16        | 53.6     | 30.4        | 91.2        | 8.8          | 0           |
|               | 70824     | 1871.34  | 2120        | 56.02       | 1054273      | 27856.47    |
|               | 19861     | 524.78   |             |             |               |             |
| Egypt         | 5.8       | 39.8     | 54.4        | 76.4        | 23.2         | 0.4         |
|               | 99712     | 974      | 5511        | 54          | 118014       | 1153.22     |
|               | 6750      | 65.96    |             |             |               |             |
| Croatia       | 11        | 42.3     | 46.7        | 93.4        | 6.4          | 0.2         |
|               | 11739     | 2859     | 197         | 48          | 147454       | 35918.25    |
|               | 2102      | 51203    |             |             |               |             |

*aRecorded on 7th Sep 2020 from WHO Coronavirus disease (COVID-19) Situation Report.

bRecorded on 6th Dec 2020 from WHO Coronavirus disease (COVID-19) Situation Report.
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. 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 positive correlation between the prevalence recorded on 7th September and AG genotype of rs2275913 in the 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. 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. 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. 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 insight 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.

**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 |
|--------------|--------|------------------------|-----------------------|
|              | Date   |                        |                       |
| 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  |
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.

ORCID

Lutfiye Karcioğlu Batur http://orcid.org/0000-0002-4803-9137

REFERENCES

1. Öztürk R, Tayova Y, Ayaz A. COVID-19: pathogenesis, genetic polymorphism, clinical features and laboratory findings. Turk J Med Sci. 2020;21, 50 (SI-1):638-657.
2. World Health Organization. Coronavirus disease (COVID-19) Weekly epidemiological update December 8, 2020. Accessed December 8, 2020. https://www.who.int/publications/m/item/weeklyepidemiological-update-8-december-2020
3. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-2629.
4. Zhou Y, Fu B, Zheng X, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. bioRxiv. 2020. 02.12.945576. https://doi.org/10.1101/2020.02.12.945576
5. Wan S, Yi Q, Fan S, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). medRxiv. 2020. 02.10.20021832. https://doi.org/10.1002/med.21832
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
7. Elhabayan A, EIyaacoub S, Sanad E, Abukhadr A, Elhabayan A, Dinu V. The role of host genetics in susceptibility to severe viral infections in humans and insights into host genetics of severe COVID-19: a systematic review. Virus Res. 2020;289:198163.
8. Mao ZR, Zhang SL, Feng B. Association of IL-10 (−819T/C, −592A/C and −1082A/G) and IL-6 -174G/C gene polymorphism and the risk of pneumonia-induced sepsis. Biomarkers. 2017;22(2):106-112.
9. Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? Nat Rev Immunol. 2020;20(6):345-346.
10. Zhang D, Xie M, Yang X, et al. Determination of IL-1B (rs16944) and IL-6 (rs1800796) genetic polymorphisms in IgA nephropathy in a northwest Chinese Han population. Oncotarget. 2017;8(42):71750-71758.
11. Sugimoto Y, Wakai K, Nakagawa H, et al. Associations between polymorphisms of interleukin-6 and related cytokine genes and serum liver damage markers: a cross-sectional study in the Japan MultiInstitutional Collaborative Cohort (J-MICC) Study. Gene. 2015; 557(2):158-162.
12. Miwa K, Okazaki S, Sakaguchi M, Mochizuki H, Kitagawa K. Interleukin-6, interleukin-6 receptor gene variant, small-vessel disease and incident dementia. Eur J Neurol, 2016;23(3):656-663.
13. Sundaresh A, Oliveira J, Chinnadurai RK, et al. IL6/IL6R genetic diversity and plasma IL6 levels in bipolar disorder: An Indo-French study. Heliyon. 2019;5(1):e01124.
14. López-Mejías R, Sevilla Pérez B, Genre F, et al. No evidence of association between functional polymorphisms located within IL6R and IL6ST genes and Henoch-Schönlein purpura. Tissue Antigens. 2013;82(6):416-419.
15. Jiménez-Sousa MA, Medrano LM, Liu P, et al. IL-6 rs1800795 polymorphism is associated with septic shock-related death in patients who underwent major surgery: a preliminary retrospective study. Ann Intensive Care. 2017;7(1):22.
16. Vargas-Alarcon G, Ramírez-Bello J, Juárez-Cedillo T, Ramírez-Fuentes S, Carrillo-Sánchez S, Fragoso JM. Distribution of the IL-1RN, IL-6, IL-10, INF-γ, and TNFα gene polymorphisms in the Mexican population. Genet Test Mol Biomarkers. 2012;16(10):1246-1253.
17. Ponce de León-Suárez V, Valdés-Flores M, Miranda-Duarte A, et al. Association of the IL6 rs1800796, but not of the IL6 rs1800795, IL6R rs4845617 and rs2228145 polymorphisms with hip fracture in elderly Mexican women. Aging Clin Exp Res. 2018;30(4):407-410.
18. Suijkerbuijk MAM, Ponzetti M, Rahim M, et al. Functional polymorphisms within the inflammatory pathway regulate expression of extracellular matrix components in a genetic risk dependent model for anterior cruciate ligament injuries. J Sci Med Sport. 2019;22(11):1219-1225.
19. Sarsu SB, Yilmaz ŞG, Bayram A, Denk A, Kargun K, Sungur MA. Polymorphisms in the IL-6 and IL-6R receptor genes as new diagnostic biomarkers of acute appendicitis: a study on two candidate genes in pediatric patients with acute appendicitis. Ital J Pediatr. 2015;41:100.
20. Vargas VR, Bonatto SL, Macagnan FE, et al. Influence of the 48867A>C (Asp358 Ala) IL6R polymorphism on response to a lifestyle modification intervention in individuals with metabolic syndrome. Genet Mol Res. 2013;12(3):3983-3991.
21. Mattos MF, Uback L, Biselli-Chicote PM, Biselli JM, Goloni-Bertilto EM, Pavarino EC. Polymorphisms of interleukin 6 in Down syndrome individuals: a case-control study. Genet Mol Res. 2017;16(3). https://doi.org/10.4238/gmr16039738
22. Topchieva LV, Kurbatova IV, Dudanova OP, Sokolovskaya AA. IL6R Gene Polymorphic Variant rs2228145(C >A) as a marker of genetic liability to nonalcoholic steatohepatitis in the Russian population of Karelia. Genet Mol Res. 2015;14(1):61-66.
23. Mitrokhin V, Nikitin A, Brovkina O, et al. Association between interleukin-6/6R gene polymorphisms and Henoch-Schönlein purpura. Tissue Antigens. 2013;82(6):416-419.
24. Vargas VR, Bonatto SL, Macagnan FE, et al. Influence of the 48867A>C (Asp358Ala) IL6R polymorphism on response to a lifestyle modification intervention in individuals with metabolic syndrome. Genet Mol Res. 2013;12(3):3983-3991.
25. Mattos MF, Uback L, Biselli-Chicote PM, Biselli JM, Goloni-Bertilto EM, Pavarino EC. Polymorphisms of interleukin 6 in Down syndrome individuals: a case-control study. Genet Mol Res. 2017;16(3). https://doi.org/10.4238/gmr16039738
26. Topchieva LV, Kurbatova IV, Dudanova OP, Sokolovskaya AA. IL6R Gene Polymorphic Variant rs2228145(C >A) as a marker of genetic liability to nonalcoholic steatohepatitis in the Russian population of Karelia. Genet Mol Res. 2015;14(1):61-66.
26. Heidema AG, Wang P, van Rossum CT, et al. Sex-specific effects of CNTF, IL6 and UCP2 polymorphisms on weight gain. Physiol Behav. 2010;12. 99 (1):1-7.

27. Platki MN, Zervou MI, Samonis G, Daraki V, Goulielmou GN, Kolteridis DP. Association of the interleukin-6 rs1800795 polymorphism with type 2 diabetes mellitus in the population of the Island of Crete, Greece. Genet Test Mol Biomarkers. 2018;22(7): 448-452.

28. Schotte H, Schlüter B, Rust S, Assmann G, Domschke W, Gaußitz M. Interleukin-6 promoter polymorphism (−174 G/C) in Caucasian German patients with systemic lupus erythematosus. Rheumatology (Oxford). 2001;40(4):393-400.

29. Fishman D, Fauds G, Jeffery R, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998;102:136-176.

30. Gao J, Wei L, Fu R, et al. Association of interleukin-10 polymorphisms (rs1800872, rs1800871, and rs1800896) with predisposition to IgA nephropathy in a Chinese Han population: a case-control study. Kidney Blood Press Res. 2017;42(1):89-98.

31. Singh R, Ghoshal UC, Kumar S, Mittal B. Genetic variants of immune-related genes IL17F and IL10 are associated with functional dyspepsia: A case-control study. Indian J Gastroenterol. 2017;36(5):343-352.

32. Mohammadi S, Saghaeian Jazi M, Zare Ebrahimabadi M, et al. Interleukin 10 gene promoter polymorphisms (rs1800896, rs1800871 and rs1800872) and haplotypes are associated with the activity of systemic lupus erythematosus and IL10 levels in an Iranian population. Int J Immunogenet. 2019:46(1):20-30.

33. López-Hernández R, Valdés M, Campillo JA, et al. Pro- and anti-inflammatory cytokine gene single-nucleotide polymorphisms in inflammatory bowel disease. Int J Immunogenet. 2015;42(1):38-45.

34. Stappers MH, Thys Y, Oosting M, et al. Polymorphisms in cytokine genes IL6, TNF, IL10, IL17A and IFNG influence susceptibility to complicated skin and skin structure infections. Eur J Clin Microbiol Infect Dis. 2014;33(12):2267-2274.

35. Bagnoli S, Cellini E, Tedde A, et al. Association of IL10 promoter polymorphism in Italian Alzheimer’s disease. Neurosci Lett. 2007;418(3):262-265.

36. Holster A, Teräsjärvi J, Vuononvirta J, et al. Polymorphisms in the promoter region of IL10 gene are associated with virus etiology of infant bronchiolitis. World J Pediatr. 2018;14(6):594-600.

37. Braz M, Oliveira JM, Rêgo JL, Carvalho EM, Santos S, Castellucci LC. Polymorphism in the interleukin-10 gene is associated with overactive bladder phenotype associated with HTLV-1 infection. Rev Soc Bras Med Trop. 2019;52:e20180481.

38. Borilova Lnhartova P, Janos J, Slezkova S, et al. Recurrent atherosclerosis and gene variability in selected interleukins: a case-control study. Eur J Oral Sci. 2018;126(6):485-492.

39. Zidi S, Gazouani E, Stayouss M, et al. IL-10 gene promoter and intron polymorphisms as genetic biomarkers of cervical cancer susceptibility among Tunisians. Cytokine. 2015;76(2):343-347.

40. Matushita M, Tanaka A, Kikuchi K, et al. Association of single nucleotide polymorphisms of the interleukin-10 promoter gene and susceptibility to primary biliary cirrhosis: immunogenetic differences in Italian and Japanese patients. Autoimmunity. 2002;35(8):531-536.

41. Mirowska-Guzel D, Gromadzka G, Mach A, Czonkowski A, Czonkowsa A. Association of IL1A, IL1B, ILRN, IL6, IL10 and TNFα polymorphisms with risk and clinical course of multiple sclerosis in a Polish population. J Neuroimmunol. 2011;236(1-2):87-92.

42. Gao L, Weck MN, Nieters A, Brenner H. Association between a pro-inflammatory genetic profile and the risk of chronic atrophic gastritis among older adults from Germany. Eur J Cancer. 2009;45(3):428-434.

43. Myhr KM, Vagnes KS, Marøy TH, Aarseth JH, Nyland HI, Vedeler CA. Interleukin-10 promoter polymorphisms in patients with multiple sclerosis. J Neurol Sci. 2002;202:93-97.

44. Wallace GR, Kondeatis E, Vaughan RW, et al. IL-10 genotype analysis in patients with Behcet's disease. Hum Immunol. 2007;68(2):122-127.

45. Wang J, Liu Y, Xie L, Li S, Qin X. Association of IL-17A and IL-17F gene polymorphisms with chronic hepatitis B and hepatitis B virus-related liver cirrhosis in a Chinese population: A case-control study. Clin Res Hepatol Gastroenterol. 2016;40(3):288-296.

46. Kasamatsu T, Kimoto M, Takahashi N, et al. IL17A and IL23R gene polymorphisms affect the clinical features and prognosis of patients with multiple myeloma. Hematol Oncol. 2018;36(1):196-201.

47. Kawaguchi M, Takahashi D, Hizawa N, et al. IL-17F sequence variant (His161Arg) is associated with protection against asthma and antagonizes wild-type IL-17F activity. J Allergy Clin Immunol. 2006;117(4):795-801.

48. Tayfesnasrabadi H, Mohebbi SR, Hosseini SM, et al. Association of Interleukin-17 gene polymorphisms with susceptibility to chronic hepatitis B virus infection and clearance in Iranian population. Microb Pathog. 2020;144:104195.

49. Prieto-Pérez R, Solano-López G, Cabaleiro T, et al. The polymorphism rs763780 in the IL-17F gene is associated with response to biological drugs in patients with psoriasis. Pharmacogenomics. 2015;16(15):1723-1731.

50. Montufar-Robles I, Barbosa-Cobos RE, Aleman-Avila I, Ramirez-Bello J. IL17A haplotype confers susceptibility to systemic lupus erythematosus but not to rheumatoid arthritis in Mexican patients. Int J Rheum Dis. 2019;22(3):473-479.

51. Escamilla-Tilch M, Estrada-Garcia I, Granados J, et al. Lack of association of the polymorphisms IL-17A (-197G/A) and IL-17F (+7488A/G) with multicentric leprosy in Mexican patients. Int J Genomics. 2014;2014:920491.

52. Akbulut UE, Çebi AH, Sağ E, İkbal M, Çakır M. Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children. Turk J Gastroenterol. 2017;28(6):471-475.

53. Pehlivan S, Aytaç HM, Kurnaz S, Pehlivan M, Çetinay Aydin P. Evaluation of COMT (rs4680), CNR2 (rs2501432), CNR2 (rs2229579), UC2P (rs59366), and IL-17 (rs763780) gene variants in synthetic cannabinoid use disorder patients. J Addict Dis. 2020;38(4):495-505.

54. Liehu-Martiskainen M, Korppi M, Teräsjärvi J, et al. Interleukin 17A gene polymorphism rs2275913 is associated with osteitis after the Bacillus Calmette-Guérin vaccination. Acta Paediatr. 2017;106(11):1837-1841.

55. Recha Loures MA, Macedo LC, Reis DM, et al. Influence of TNF and IL17 Gene Polymorphisms on the spondyloarthriss immunopathogenesis, regardless of HLA-B27, in a Brazilian population. Mediators Inflamm. 2018;2018:1395823.

56. Navratilova Z, Galo J, Mrazek F, Petrek M. Genetic variation in TH17 immune response is not associated with risk for prosthetic joint infection in a Czech population. J Biomed Bioeng. 2018;45(5):1563-1570.

57. Poomarimuthu M, Elango S, Solomon PR, Soundarpandian S, Mariakuttikan J. Association of IL17 and IL23R gene polymorphisms with rheumatic heart disease in South Indian population. Immunol Invest. 2018;47(7):754-764.

58. Schieck M, Michel S, Suttner K, et al. Genetic variation in TH17 pathway genes, childhood asthma, and total serum IgE levels [letter]. J Allergy Clin Immunol. 2014;133:888-891.

59. Nordang GB, Viken MK, Hollis-Moffatt JE, et al. Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology (Oxford). 2009;48(4):367-370.
60. Maalmi H, Beraies A, Charad R, Ammar J, Hamzaoui K, Hamzaoui A. IL-17A and IL17F genes variants and susceptibility to childhood asthma in Tunisia. J Asthma. 2014;51:348-354.

61. Wróbel T, Gębura K, Wysoczańska B, et al. IL-17F gene polymorphism is associated with susceptibility to acute myeloid leukemia. J Cancer Res Clin Oncol. 2014;140(9):1551-1555.

62. Hammad A, Mosaad YM, Hammad EM, et al. Interleukin-17A rs2275913, Interleukin-17F rs763780 and rs2397084 gene polymorphisms as possible risk factors in Juvenile lupus and lupus related nephritis. Autoimmunity. 2016;49(1):31-40.

63. Vrgoc G, Vrbanec J, Eftedal RK, et al. Interleukin-17 and Toll-like Receptor 10 genetic polymorphisms and susceptibility to large joint osteoarthritis. J Orthop Res. 2018;36(6):1684-1693.

64. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954.

65. Riazalhosseini B, Mohamed Z, Apalasamy YD, Shafie NS, Mohamed R. Interleukin-6 gene variants are associated with reduced risk of chronicity in hepatitis B virus infection in a Malaysian population. Biomed Rep. 2018;9(3):213-220.

66. Ulhaq ZS, Soraya GV. Anti-IL-6 receptor antibody treatment for severe COVID-19 and the potential implication of IL-6 gene polymorphisms in novel coronavirus pneumonia. Tratamiento con anticuerpos anti-receptor de IL-6 para COVID-19 grave y la posible implicación de polimorfismos del gen IL-6 en la nueva neumonía por coronavirus. Med Clin (Barc). 2020;155(12):548-556.

67. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062.

68. Chong WP, Ip WK, Tso GH, et al. The interferon gamma gene polymorphism +874 A/T is associated with severe acute respiratory syndrome. BMC Infect Dis. 2006;6:82.

69. Lau YL, Peiris JS. Association of cytokine and chemokine gene polymorphisms with severe acute respiratory syndrome. Hong Kong Med J. 2009;15:43-46.

70. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China: Life Sci. 2020;63(3):364-374.

71. Xie M, Cheng B, Ding Y, Wang C, Chen J. Correlations of IL-17 and NF-kB gene polymorphisms with susceptibility and prognosis in acute respiratory distress syndrome in a Chinese population. Biosci Rep. 2019;39(2):BSR20181987.

72. Mikacenic C, Hansen EE, Radella F, Gharib SA, Stapleton RD, Wurfel MM. Interleukin-17A is associated with alveolar inflammation and poor outcomes in acute respiratory distress syndrome. Crit Care Med. 2016;44(3):496-502.

73. Ren W, Wu Z, Ma R, et al. Polymorphisms in the IL17 gene (rs2275913 and rs763780) are associated with hepatitis B virus infection in the Han Chinese population. Genet Test Mol Biomarkers. 2017;21(5):286-291.

74. Ma WT, Yao XT, Peng Q, Chen DK. The protective and pathogenic roles of IL-17 in viral infections: friend or foe? Open Biol. 2019;9:190109.

75. Christensen-Quick A, Lafferty M, Sun L, Marchionni L, DeVico A, Garzino-Demo A. Human TH17 cells lack HIV-inhibitory RNases and are highly permissive to productive HIV infection. J Virol. 2016;90:7833-7847.

76. Gopal R, Rangel-Moreno J, Fallert Junecko BA, et al. Mucosal pre-exposure to Th17-inducing adjuvants exacerbates pathology after influenza infection. Am J Pathol. 2014;184(1):55-63.

SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Karcioğlu Batur L, Hekim N. Correlation between interleukin gene polymorphisms and current prevalence and mortality rates due to novel coronavirus disease 2019 (COVID-2019) in 23 countries. J Med Virol. 2021;1-11. https://doi.org/10.1002/jmv.27127