# Correlation of the variations in prevalence of coronavirus disease 2019 and vitamin D receptor gene polymorphisms in cohorts from 26 countries

## Yirmi altı ülkeden kohortlarda koronavirüs hastalığı 2019 prevalansındaki varyasyonların vitamin D reseptör gen polimorfizmleriyle korelasyonu

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**Abstract**

**Aim:** This study aimed to investigate the correlation between the rates of coronavirus disease 2019 (COVID-19) prevalence and mortality and the frequency of vitamin D receptor (VDR) gene polymorphisms at the loci rs7975232 (*ApaI*), rs1544410 (*BsmI*), rs2228570 (*FokI*), and rs731236 (*TaqI*) in cohorts from 26 countries.

**Methods:** The study included the use of 26 countries where VDR gene polymorphisms at the loci rs731236 (*TaqI*), rs7975232 (*ApaI*), rs2228570 (*FokI*), and rs1544410 (*BsmI*) were determined and where the relevant frequencies of alleles in healthy populations were reported: Italy, China, Turkey, Japan, Mexico, Russia, India, Poland, Egypt, Czechia, Ethiopia, Saudi Arabia, Greece, the Netherlands, Korea, Spain, the United States, Pakistan, Nigeria, Lebanon, the Central African Republic, Finland, Iran, Tunisia, Brazil, and Croatia. The COVID-19 prevalence and mortality rates (per million population) reported for each country on 6 December 2020 were recorded.

**Results:** A significant positive correlation was found between the frequency of AA genotype of rs7975232 and the COVID-19 prevalence (r=0.45, r2=0.20, p=0.02) and mortality (r=0.42, r2=0.17, p=0.03) rates. Twenty percent of the variability in prevalence and 17% of the variability in mortality could be explained by the frequency of AA genotype. Similarly, a significant positive correlation was found between the frequency of TT genotype of rs731236 and the COVID-19 prevalence (r=0.42, r2=0.17, p=0.03) rates. Seventeen percent of the variability in prevalence could be explained by the frequency of TT genotype. The correlations between the frequency of rs1544410 and rs2228570 and the COVID-19 prevalence and mortality were not significant.

**Conclusion:** The variation in COVID-19 prevalence in the 26 populations included can be explained by the polymorphisms at the rs7975232 (*ApaI*) and rs731236 (*TaqI*) loci.

**Keywords:** coronavirus disease 2019; correlation; polymorphism; vitamin D receptor

**Öz**

**Amaç:** Bu çalışmada 26 ülkeden kohortlarda rs7975232 (*ApaI*), rs1544410 (*BsmI*), rs2228570 (*FokI*), rs731236 (*TaqI*) lokuslarında vitamin D reseptör (VDR) gen polimorfizmi sıklığı ile koronavirüs hastalığı 2019 (*COVID-19*) prevalans ve mortalite oranları arasındaki korelasyonu araştırmak amaçlanmıştır.

**Yöntem:** Çalışmada rs7975232 (*ApaI*), rs2228570 (*FokI*), rs1544410 (*BsmI*) ve rs731236 (*TaqI*) lokuslarında VDR gen polimorfizmleri tanımlanmış ve sağlıklı popülasyonlarda ilgili alel frekansları bildirilmiş 26 ülke kullanıldı: İtalya, Çin, Türkiye, Japonya, Meksika, Rusya, Hindistan, Polonya, Mısır, Çekya, Etiyopya, Suudi Arabistan, Yunanistan, Hollanda, Kore, İspanya, Birleşik Devletler, Pakistan, Nijerya, Lübnan, Orta Afrika Cumhuriyeti, Finlandiya, İran, Tunus, Brezilya ve Hırvatistan. Her ülke için 6 Aralık 2020 tarihinde bildirilen COVID-19 (milyon popülasyonda) prevalans ve mortalite oranları kaydedildi.

**Bulgular:** rs7975232'nin AA genotipi sıklığı ile *COVID-19* prevalans (r=0,45; r2=0,20; p=0,02) ve mortalite (r=0,42; r2=0,17; p=0,03) oranları arasında anlamlı pozitif korelasyon saptandı. Prevalanstaki değişkenliğin %20'si ve mortalitedeki değişkenliğin %17'si AA genotipinin sıklığı ile açıklanabildi. Yine rs731236'nın TT genotipi ile COVID-19 prevalans (r=0,42; r2=0,17; p=0,03) oranları arasında anlamlı pozitif korelasyon saptandı. Prevalanstaki değişkenliğin %17'si TT genotipinin sıklığı ile açıklanabildi. rs1544410 ve rs2228570 sıklığı ile COVID-19 prevalans ve mortalitesi arasındaki korelasyonlar anlamlı değildi.

**Sonuç:** İncelenen 26 popülasyondaki *COVID-19* prevalans varyasyonları rs7975232 ve rs731236 lokuslarındaki polimorfizmler ile açıklanabilir.

**Anahtar sözcükler:** D vitamini reseptörü; korelasyon; koronavirüs hastalığı 2019; polimorfizm

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## INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a serious health concern worldwide (1). According to the World Health Organization (WHO) reports, the global number of confirmed cases and deaths reached 65 million and 1.5 million by 6 December 2020, respectively (2). In Turkey, more than 533 thousand cases and 14 thousand deaths were recorded by the same date (2). There have been extensive global and national attempts to develop vaccines for use against the rapid transmission of the infection. However, the severity of infection, comorbidities found in patients, and variations in the genetic background of patients result in differences in the course, progression and complications of the disease (1–4).

Vitamin D deficiency (VDD) has been linked to the risk of upper respiratory infection. With findings that vitamin D supplementation reduces this risk by about 19% (5), it is speculated that vitamin D supplementation might be beneficial for COVID-19 patients with severe VDD (4). Although the underlying mechanisms of the role of VDD in viral infections are not adequately understood, it is known that several types of tissues and cells produce 1,25-dihydroxyvitamin D3 ($1,25[OH]_2D_3$), the active form of vitamin D, which is subsequently recognized by the vitamin D receptor (VDR). Many of the biological impacts of $1,25(OH)_2D_3$ are adjusted by binding to the VDR and allowing the activation and regulation of multiple cellular pathways (6). Several reports have proposed that the signaling pathway between vitamin D and VDR may ameliorate the lipopolysaccharide-induced acute respiratory distress syndrome (ARDS), the main complication in COVID-19, which is regulated via several mechanisms including the reduction of cytokines and chemokines, modulation of neutrophil activity, stimulation of epithelial repair, and protection of the unity of pulmonary epithelial barrier (7,8). Based on these reports, ARDS may be provoked by VDD and diminished by the stimulation of VDR pathways in COVID-19 (4).

Various genetic polymorphisms have been implicated in the underlying mechanisms of several diseases, prevention of the spread of infections, and development of effective therapies. Single-nucleotide polymorphisms (SNPs) are commonly suggested to play a role in the host cell invasion mechanisms of microbiological agents, disease severity, and host resistance and sensitivity (1). Severe symptoms of COVID-19 have been widely reported to be correlated with variants of genes encoding the vitamin D binding protein (VDBP), VDR, and agents of the host defense system (9,10). Recently, we reported that variations in the COVID-19 prevalence and mortality might be related to VDBP polymorphisms located at the rs7041 and rs4588 loci (10).

SNPs in genes encoding proteins of the vitamin D metabolism are related to the severity of several viral infections or the success of protections against those infections (11). SNPs located in VDR genes are associated with infectious and autoimmune diseases (12). The rs1544410 (*BsmI*) polymorphism was found to be associated with increased resistance to HIV infection and delayed progression of acquired immunodeficiency syndrome (AIDS), suggesting an increased response to vitamin D (13). Other VDR-SNPs have been shown to be associated with distinct clinical phenotypes and different degrees of severity of hepatitis B infection (14). Therefore, genetic variation in the vitamin D metabolism has paramount importance in understanding the association between VDD and the course, prognosis, and mortality of viral infections, including COVID-19. Accordingly, this study involving cohorts from 26 countries aimed to investigate the correlation between the frequency of VDR gene polymorphisms at the loci rs7975232 (*ApaI*), rs2228570 (*FokI*), rs1544410 (*BsmI*), and rs731236 (*TaqI*) (the four most common VDR-SNPs) and the COVID-19 prevalence and mortality.

## MATERIALS AND METHODS

In order to reduce confounding bias (geographical, age, sex, race, etc.), the study included the use of countries where VDR gene polymorphisms at the loci rs7975232 (*ApaI*), rs2228570 (*FokI*), rs1544410 (*BsmI*), and rs731236 (*TaqI*) were determined and where the relevant allele frequencies in healthy cohorts were reported. The following 26 countries were included: Italy, China, Turkey, Japan, Mexico, Russia, India, Poland, Egypt, Czechia, Ethiopia, Saudi Arabia, Greece, the Netherlands, Korea, Spain, the

**Table 1.** Genotype frequencies of the VDR polymorphisms at the loci rs1544410 *(BsmI)*, rs2228570 *(FokI)*, rs7975232 *(ApaI)*, and rs731236 *(TaqI)* and the COVID-19 prevalence and mortality for each country as reported by WHO on 6 December 2020.

| | rs1544410 (*BsmI*) | | rs2228570 (*FokI*) | | rs7975232 (*ApaI*) | | | rs731236 (*TaqI*) | | | Prevalence* | | Mortality | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | *AA (BB)* | *AG (Bb)* | *GG (bb)* | *CC (FF)* | *CT (Ff)* | *TT (ff)* | *AA* | *AC* | *CC* | *TT* | *CT* | *CC* | *Total* | *per million* | *Total* | *per million* | **Reference** |
| Italy | 11.2 | 50 | 38.8 | 54.8 | 30.5 | 5.7 | 45.5 | 41 | 13.4 | 39.1 | 44.2 | 16.6 | 1709991 | 28282 | 59514 | 984 | Tanaka et al. (15), Conti et al. (16) |
| China | 17.2 | 48.7 | 34.1 | 29 | 51 | 20 | 12 | 41 | 47 | 90 | 0.09 | 0.01 | 94160 | 64 | 4753 | 3.23 | Xia et al. (17), Fan et al. (18) |
| Turkey | 33 | 52 | 15 | 10 | 40 | 50 | 43.3 | 33.3 | 23.4 | 43.3 | 36.7 | 20 | 533198 | 6322 | 14705 | 174.36 | Dal et al. (19) |
| Japan | 1.7 | 16.8 | 81.5 | 39.5 | 47.3 | 13.2 | 9 | 43.7 | 47.3 | 79.6 | 18.8 | 1.7 | 160098 | 1266 | 2315 | 18.3 | Tanaka et al. (20) |
| Mexico | 4.5 | 43.2 | 52.3 | 27.3 | 51.1 | 21.6 | 19.6 | 47.1 | 33.3 | 52.3 | 40.9 | 6.8 | 1156770 | 8972 | 108863 | 844.34 | González-Mercado et al. (21) |
| Russia | 21.7 | 54.2 | 24.1 | 28.4 | 42.7 | 45.1 | 25.1 | 54.9 | 20 | 45.1 | 42.7 | 28.4 | 2460770 | 16862 | 43141 | 295.62 | Kondratyeva et al. (22) |
| India | 25.7 | 42.9 | 31.4 | 51.4 | 39 | 9.5 | 24.8 | 50.5 | 24.8 | 42.9 | 51.4 | 5.7 | 9644222 | 6989 | 140182 | 101.58 | Alagarasu et al. (23) |
| Poland | 33 | 53 | 15 | 40 | 43 | 22 | 27 | 48 | 25 | 25 | 57 | 18 | 1054273 | 27856 | 19861 | 524.78 | Cieślińska et al. (24) |

* The prevalence of a health condition is the number of individuals who have the condition at the moment of observation.

| The United States | Spain | Korea | The Netherlands | Greece | Saudi Arabia | Ethiopia | Czechia | Egypt |
|---|---|---|---|---|---|---|---|---|
| 9.8 | 20.5 | 0 | 16.6 | 0 | 23 | - | 15.1 | 26 |
| 49.6 | 42.9 | 13.8 | 47.9 | 68 | 39 | - | 44.8 | 52 |
| 40.7 | 36.6 | 86.3 | 35.5 | 32 | 38 | - | 40.1 | 22 |
| 40.8 | 48.2 | 31.3 | 40.2 | 46.7 | 58 | 54 | 30.6 | 8 |
| 45.6 | 40.2 | 46.3 | 45.6 | 41.7 | 37 | 39.6 | 49.4 | 28 |
| 13.6 | 11.6 | 22.5 | 14.2 | 11.7 | 5 | 6.4 | 20 | 64 |
| 29.8 | 37.2 | 8 | 27.7 | 24 | 45 | 43.7 | 24.4 | 42.5 |
| 46.8 | 43 | 30.1 | 51.9 | 60.4 | 23 | 42.2 | 50.6 | 37.5 |
| 23.4 | 19.5 | 61.9 | 20.4 | 15.6 | 32 | 14.1 | 25 | 20 |
| 39.5 | 44.5 | 92.9 | 38.8 | 44.8 | 43 | 38.3 | 40.5 | 24 |
| 46.8 | 33.3 | 7.1 | 47.7 | 44.4 | 41 | 42.5 | 45 | 32 |
| 13.7 | 22.2 | 0 | 13.5 | 14.8 | 16 | 19.2 | 14.5 | 44 |
| 14191298 | 1684647 | 37546 | 549784 | 114568 | 358526 | 112760 | 544179 | 118014 |
| 42874 | 36031.6 | 732 | 32086 | 10992 | 10298 | 981 | 50815 | 1153 |
| 276503 | 46252 | 545 | 9649 | 2902 | 5954 | 1745 | 8815 | 6750 |
| 835.35 | 989.25 | 10.63 | 563.12 | 278.42 | 171.02 | 15.18 | 823.14 | 65.96 |
| Clendenen et al. (36) | Gisbert-Ferrándiz et al. (34), Jiménez-Sousa et al. (35) | Ahn et al. (33) | Lanjouw et al. (31), Smolders et al. (32) | Panierakis et al. (30) | Alkhayal et al. (29) | Ahmed et al. (28) | Hughes et al. (26), Pleva et al. (27) | Mostafa-Hedeab et al. (25) |

| Croatia | Brazil | Tunisia | Iran | Finland | The Central African Republic | Lebanon | Nigeria | Pakistan |
|---|---|---|---|---|---|---|---|---|
| 9.2 | 12.7 | 16.7 | 28.89 | 12 | 38.02 | 36.7 | 15 | 0 |
| 52 | 48.7 | 53.6 | 34.44 | 37 | 46.47 | 51.89 | 44 | 0 |
| 37.8 | 38.6 | 30 | 36.67 | 51 | 15.49 | 11.39 | 41 | 100 |
| 30.2 | 44 | 41.4 | 56 | 43.48 | 22 | 56.6 | 58 | 0 |
| 57.1 | 48 | 47.9 | 36 | 45.65 | 44 | 39.6 | 32 | 0 |
| 16.6 | 9 | 10.7 | 9 | 10.87 | 34 | 3.8 | 10 | 100 |
| 19 | 29 | 35.7 | 33 | 21.74 | 42 | 48.2 | 47 | 99.8 |
| 52.9 | 53.8 | 47.9 | 53.3 | 58.7 | 46.1 | 34.7 | 36 | 0.2 |
| 28.6 | 16.8 | 16.4 | 13.4 | 19.57 | 11.9 | 17.1 | 17 | 0 |
| 47 | 41.1 | 35 | 42.22 | 50.4 | 38.57 | 6.32 | 53 | 3.6 |
| 45.4 | 48.2 | 52.1 | 45.56 | 37.2 | 47.14 | 60.75 | 42 | 96.4 |
| 7.6 | 10.7 | 12.9 | 12.22 | 12.3 | 14.28 | 32.91 | 5 | 0 |
| 147454 | 6533968 | 102991 | 1028986 | 27218 | 4922 | 135876 | 68937 | 413191 |
| 35918 | 30739.49 | 8714 | 12250.85 | 4912 | 1019 | 19907 | 334 | 1871 |
| 2102 | 175964 | 3526 | 50016 | 415 | 63 | 1090 | 1180 | 8303 |
| 512.03 | 827.83 | 298.34 | 595.48 | 74.9 | 13.04 | 159.7 | 5.72 | 37.59 |
| Gašparović et al. (45) | Neves et al. (44) | Kaabachi et al. (43) | Rashedi et al. (42) | Heikkinen et al. (41) | Bornman et al. (40) | Hajj et al. (39) | Fischer et al. (38) | Mukhtar et al. (37) |

**Table 2.** Correlation between the frequencies of the VDR polymorphisms at the loci rs1544410 *(BsmI)*, rs2228570 *(FokI)*, rs7975232 *(ApaI)*, and rs731236 *(TaqI)* and the COVID-19 prevalence and mortality in all cohorts

| VDR polymorphism | Genotype | Prevalence per million | | Mortality per million | |
|---|---|---|---|---|---|
| | | r | *p* | r | *p* |
| rs1544410 (*Bsm*I) | AA | -0.01 | 0.97 | -0.05 | 0.82 |
| | AG | 0.29 | 0.16 | 0.24 | 0.26 |
| | GG | -0.08 | 0.72 | 0.01 | 0.99 |
| rs2228570 (*Fok*I) | CC | 0.17 | 0.40 | 0.14 | 0.50 |
| | CT | 0.19 | 0.35 | 0.16 | 0.43 |
| | TT | -0.19 | 0.35 | -0.17 | 0.39 |
| rs7975232 (*Apa*I) | AA | 0.45 | *0.02* | 0.42 | *0.03* |
| | AC | -0.02 | 0.93 | -0.01 | 0.98 |
| | CC | 0.01 | 0.99 | -0.06 | 0.76 |
| rs731236 (*TaqI*) | TT | 0.42 | *0.03* | 0.27 | 0.17 |
| | CT | -0.24 | 0.24 | -0.18 | 0.39 |
| | CC | 0.35 | 0.08 | 0.31 | 0.12 |

r: Spearman's rho; VDR: vitamin D receptor

United States (US), Pakistan, Nigeria, Lebanon, the Central African Republic (CAR), Finland, Iran, Tunisia, Brazil, and Croatia (15–45). The total number of confirmed cases and number of confirmed cases per million population reported in the WHO Weekly Epidemiological Update—6 December 2020 were used as the COVID-19 prevalence and mortality data on each country (2).

### Statistical analysis

Statistical analysis was performed using the SPSS (v. 22) software. Normality of the data was checked using the Shapiro–Wilk test with kurtosis and skewness values. The amount of data in each group being insufficient, the variables did not show normal distribution. Spearman's correlation coefficient (rho) was used to assess the relationship between independent variables. $p<0.05$ was considered statistically significant.

### Study ethics

No ethical approval was sought because of the nature of the study.

## RESULTS

The diversities of rs1544410 (*BsmI)* polymorphism indicated that the cohorts of Italy, China, Russia, India, Poland, Turkey, Egypt, Czechia, Saudi Arabia, Greece, the Netherlands, Spain, the US, Nigeria, Lebanon, the CAR, Tunisia, Brazil, and Croatia frequently had the AG (Bb) genotype whereas the cohorts of Japan, Mexico, Korea, Pakistan, Finland, and Iran frequently had the GG (bb) genotype (Table 1). The frequencies of rs2228570 (*FokI)* polymorphism indicated that the cohorts of Italy, Ethiopia, Saudi Arabia, Greece, Spain, Nigeria, India, Lebanon, and Iran frequently had the CC (FF) genotype while the cohorts of China, Japan, Mexico, Poland, Czechia, the Netherlands, Korea, the US, the CAR, Finland, Tunisia, Brazil, and Croatia frequently had the CT (Ff) genotype. The cohorts of Turkey, Russia, Egypt, and Pakistan had the highest frequency of TT (ff) genotype of the rs2228570 locus (Table 1).

The frequencies of rs7975232 (*ApaI)* polymorphism indicated that the cohorts of Italy, Turkey, Egypt, Ethiopia, Saudi Arabia, Pakistan, Nigeria, and Lebanon frequently had the AA genotype whereas the cohorts of Mexico, Russia, India, Poland, Czechia, Greece, the Netherlands, Spain, the US, the CAR, Finland, Iran, Tunisia, Brazil, and Croatia frequently had the AC genotype. The cohorts of China, Japan, and Korea had the highest frequencies of CC genotype of the rs7975232 locus (Table 1). The diversities of rs731236 (*TaqI)* polymorphism indicated that the cohorts of China, Turkey, Japan, Mexico, Russia, Saudi Arabia, Greece, Korea, Spain, Nigeria, Finland, and Croatia

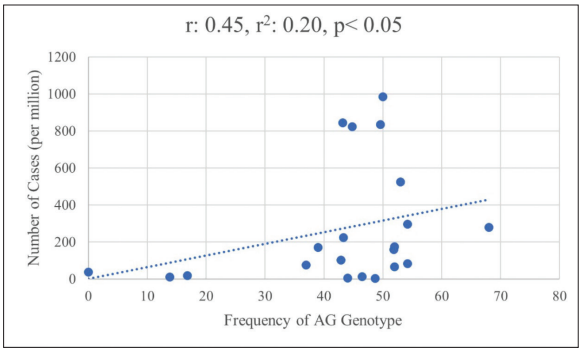


**Figure 1.** Spearman's rank correlation analysis of the relationship between COVID-19 prevalence and the frequency of AA genotype of rs7975232 (*ApaI*) recorded in each population

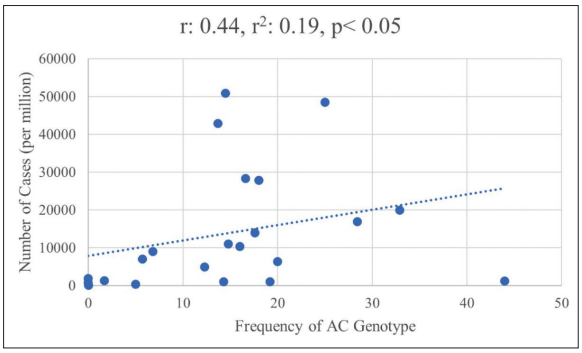


**Figure 2.** Spearman's rank correlation analysis of the relationship between COVID-19 mortality and the frequency of AA genotype at rs7975232 (*ApaI*) recorded in each population

frequently had the TT genotype whereas the cohorts of Italy, India, Poland, Czechia, Ethiopia, the Netherlands, the US, Pakistan, Lebanon, the CAR, Iran, Tunisia, and Brazil frequently had the CT genotype. Only the Egyptian cohort had a high frequency of CC genotype of the rs731236 locus (Table 1).

According to the total COVID-19 prevalence and mortality for each country as reported on 6 December 2020, Czechia and the US had the highest number of cases per million population while Spain and Italy had the highest mortality per million (Table 1).

The association between the rs1544410 (*BsmI*) and rs2228570 (*FokI*) polymorphism frequencies and the COVID-19 prevalence and mortality figures indicated that the COVID-19 figures were not significantly correlated with the frequency of any genotype ($p>0.05$) (Table 2).

The association between the frequencies of rs7975232 (*ApaI)* polymorphism and the rates of COVID-19 prevalence and mortality indicated a positive correlation between the frequency of AA genotype and the number of confirmed cases per million ($r=0.45$, $r^2=0.20$, $p=0.02$) and the rate of mortality per million ($r=0.42$, $r^2=0.17$, $p=0.03$). However, there was no significant correlation with the other genotypes of rs7975232 polymorphism (Table 2). Twenty percent of the variability in prevalence and 17% of the diversity in mortality could be explained by the frequency of AA genotype of rs7975232 reported for the selected cohorts (Figure 1 and 2).

Similarly, the association between the frequencies of rs731236 (*TaqI)* polymorphism and the prevalence and mortality data on each country indicated a positive correlation between COVID-19 prevalence and the frequency of TT genotype ($r=0.42$, $r^2=0.17$, $p=0.03$). Seventeen percent of the variability in prevalence could be explained by the frequency of TT genotype of rs731236 (Figure 3). However, no significant correlation was found with the other genotypes of rs731236 polymorphism (Table 2). No correlation was found between mortality and alleles of the rs731236 locus (Table 2).

## DISCUSSION AND CONCLUSION

In the present study, the frequencies of AA genotype of rs7975232 (*ApaI*) and TT genotype of rs731236 (*TaqI*) were found to be correlated with COVID-19 prevalence in all of the 26 cohorts, especially those from Italy, Turkey, Egypt, Ethiopia, Saudi Arabia, Pakistan, Nigeria, and Lebanon, of which the frequent genotype was the AA genotype of rs7975232, and those from China, Turkey, Japan, Mexico, Russia, Saudi Arabia, Greece, Korea, Spain, Nigeria, Finland, and Croatia, of which the frequent genotype was the TT genotype of rs731236. The AA genotype of rs7975232 (*ApaI*) SNP was also found to be correlated with mortality in all cohorts. However, SNPs at the particular loci of *BsmI* and *FokI* might not be correlated with COVID-19 prevalence and mortality. Although the frequencies of *ApaI* and *TaqI* gene polymorphisms might not be directly linked to COVID-19 prognosis and severity, current findings suggest that the *ApaI* and *TaqI* allele carrier status may be linked to diversities in the COVID-19 prevalence and mortality. This correlation analysis supports the assumption that certain VDR polymorphisms play a crucial role in the uncontrolled

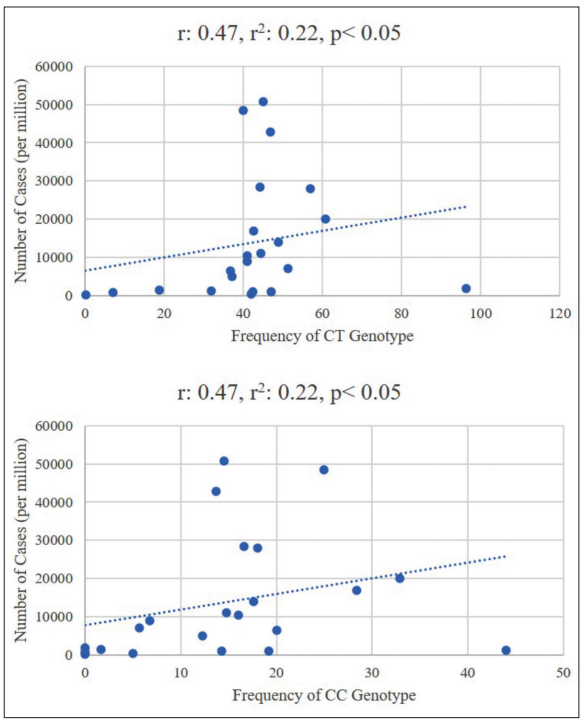


**Figure 3.** Spearman's rank correlation analysis of the relationship between COVID-19 prevalence and the frequency of TT genotype at rs731236 (*TaqI*) recorded in each population

spread and high mortality worldwide despite the extensive measures taken and vaccines being used.

The secretion of several cytokines from immune cells is mediated by the control of $1,25(OH)_2D_3$ as VDR is expressed in all immune cells. In fact, $1,25(OH)_2D_3$ stimulates the innate immune defense system by allowing the attenuation of the acquired immune system (46). Furthermore, monocytic and antigen-presenting cells can express CYP27B1 for the auto/paracrine production of $1,25(OH)_2D_3$ in the immune system. In addition, the respiratory epithelium expresses VDR and CYP27B1, suggesting being a target tissue for products of the vitamin D endocrine system (47). The risk of upper respiratory infections arises in patients with VDD and, accordingly, vitamin D supplementation may reduce that risk (5). Thus, there may be a number of possible associations between viral infections including COVID-19 and the vitamin D status of patients (4), despite the lack of reports on the correlation between frequency of VDR gene variants and COVID-19 prevalence and mortality. In our study, a significant positive correlation was found between the frequency of AA genotype of rs7975232 and the COVID-19 prevalence and mortality, and 20% of the variability in prevalence and 17% of the variability in mortality could be explained by the variation in the frequency of AA genotype. Moreover, a significant positive correlation was found between the frequency of TT genotype of rs731236 and the COVID-19 prevalence, and 17% of the variability in prevalence could be explained by the diversity in the frequency of TT genotype. Briefly, the VDR gene variation among nations may be associated with COVID-19 prevalence. No significant correlation was found between the frequencies of variants at the rs1544410 and rs2228570 loci and the COVID-19 prevalence and mortality. This may result from the variation in immune profiles based on the genetic background. Therefore, the role of the *BsmI* and *FokI* genes cannot be excluded from the predisposition genes for the disease as other SNPs in VDR genes may also take part in the regulation of subsequent gene expression. Further correlation studies on those other SNPs are needed to determine the association between VDR gene regulation and COVID-19 severity and progression.

It is important to elucidate the underlying mechanisms of genetic background variation which result in diversities in the national COVID-19 prevalence and mortality since the data on the infection are limited. Moreover, the variation observed between studies could be caused by different patient ethnicities in a given country and the use of different study designs with different sample sizes and/or control groups. Nevertheless, there is an increasing body of data suggesting that the vitamin D metabolism actively takes part in the antiviral immune responses (48). The role of the vitamin D axis including vitamin D metabolites, VDBP, and VDR was reported in respiratory diseases including ARDS, chronic obstructive pulmonary disease, and tuberculosis (49). If the vitamin D axis participates in the COVID-19 pathogenesis, variation in VDR genes could be related to host resistance or predisposition to the infection. However, it is still required to clarify the connection between VDR gene polymorphisms and the increased risk of COVID-19 in each population. Therefore, our findings can help to elucidate the host genetic background which may have a role in the variation in COVID-19 prevalence and mortality among cohorts.

Finally, the present study has several limitations, including the assumption that VDR polymorphisms in the selected samples follow the same frequencies as the cohorts reported in previous studies. Furthermore, the present study did not have complete data for all countries included in terms of all frequencies of three alleles of the four VDR genes investigated. Another limitation is that the WHO data used for COVID-19 prevalence and mortality were valid only for the date of publication; the figures have since been increasing around the world. In addition, the study included no measurement of serum or tissue levels of VDR in healthy controls for comparison with those in COVID-19 patients. However, the present findings pertaining to 26 countries suggest a potential correlation between VDR gene polymorphisms and COVID-19 prevalence, although ethnicity, age and sex differences, comorbidities, and the size of the sample recruited from each population may change the frequencies reported in different studies. In the present study, some of these effects were reduced by the use of current data from recent studies with large and various samples, as in a previous study on the correlation between interleukin gene polymorphisms and COVID-19 prevalence and mortality in 23 countries (50). However, even the frequencies for healthy subjects selected from specific regions within the same country may differ. All of these limitations can be reduced by measuring mean VDR levels, determining VDR gene allele frequencies, and assessing the correlation with the COVID-19 progression and severity in a given population, although such studies are currently lacking.

In conclusion, the correlation between frequencies of VDR gene polymorphisms and COVID-19 prevalence and mortality may depend on genetic factors involving the immune profiling, the host defense system, and the highly polymorphic VDR gene structure. Aside from genetic background, the prevalence of COVID-19 does not represent the severity of COVID-19, with other factors affecting the number of cases in each country, including the antiepidemic measures taken and the social attitude toward the vaccines. It is plausible to suggest that genetic variations in genes expressing vitamin D metabolites and the activity of those metabolites may influence the predisposition, progression, and outcomes of COVID-19 infection. Further studies with larger samples of infected individuals are required to clarify the role of the vitamin D metabolism and genetic variations in COVID-19 severity and progression.

### Conflict-of-interest and financial disclosure

The author declares that she has no conflict of interest to disclose. The author also declares that she did not receive any financial support for the study.

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