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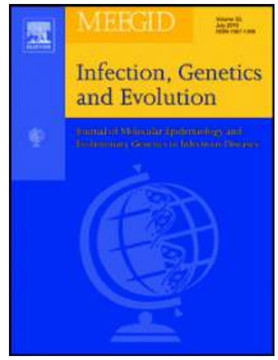

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Association of Vitamin D receptor gene polymorphisms and clinical/severe outcomes of COVID-19 patients

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Abstract

Introduction: Growing evidence documented the critical impacts of vitamin D (VD) in the prognosis of COVID-19 patients. The functions of VD are dependent on the vitamin D receptor (VDR) in the VD/VDR signaling pathway. Therefore, we aimed to assess the association of VDR gene polymorphisms with COVID-19 outcomes.

Methods: In the present study, eight VDR single nucleotide polymorphisms (SNPs) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in 500 COVID-19 patients in Iran, including 160 asymptomatic, 250 mild/moderate, and 90 severe/critical cases. The association of these polymorphisms with severity, clinical outcomes, and comorbidities were evaluated through the calculation of the Odds ratio (OR).

Results: Interestingly, significant associations were disclosed for some of the SNP-related alleles and/or genotypes in one or more genetic models with different clinical data in COVID-19 patients. Significant association of VDR-SNPs with signs, symptoms, and comorbidities was as follows: ApaI with shortness of breath ($P < 0.001$) and asthma ($P = 0.034$) in severe/critical patients (group III); BsmI with chronic renal disease ($P = 0.010$) in mild/ moderate patients (group II); Tru9I with vomiting ($P = 0.031$), shortness of breath ($P = 0.04$), and hypertension ($P = 0.030$); FokI with fever and hypertension ($P = 0.027$) in severe/critical patients (group III); CDX2 with shortness of breath ($P = 0.022$), hypertension ($P = 0.036$), and diabetes ($P = 0.042$) in severe/critical patients (group III); EcoRV with diabetes ($P < 0.001$ and $P = 0.045$ in mild/ moderate patients (group II) and severe/critical patients (group III), respectively). However, the association of VDR TaqI and BglI polymorphisms with clinical symptoms and comorbidities in COVID-19 patients was not significant.

Conclusion: VDR gene polymorphisms might play critical roles in the vulnerability to infection and severity of COVID-19, probably by altering the risk of comorbidities. However, these results require further validation in larger studies with different ethnicities and geographical regions.

Keywords: COVID-19, Vitamin D Receptor, Single nucleotide polymorphisms (SNPs), Genetic predisposition, Clinical outcomes

Introduction

The ongoing global epidemic of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, certainly represents one of the most important clinical emergencies of the 21st century (1, 2). COVID-19 can manifest a wide spectrum of clinical symptoms, which range from lack of symptoms, or mild symptoms of the upper respiratory tract to severe pneumonia with acute respiratory distress syndrome (ARDS) and death (3, 4). This highly phenotypic heterogeneity seems to depend on patient age, gender, underlying health conditions, and inter-individual genetic unevenness (5). Vitamin D (VD) has been demonstrated to perform critical roles in a wide range of immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant functions. Therefore, its deficiency and insufficiency contribute to many pathogenic conditions, including autoimmune disorders, respiratory infections, cancer, cardiovascular disorders, osteoporosis, sarcopenia, and diabetes (6-9). There is growing evidence to indicate that VD insufficiency is strongly associated with an increased risk of acquiring COVID-19 infection (10), as well as developing COVID-19-associated thrombosis (11). Furthermore, VD deficiency was demonstrated to be a fatal co-morbidity in COVID-19 patients (12). On the other hand, mounting investigations declare that VD supplementation, especially FDA-approved analog (generic name, paricalcitol), prevents COVID-19 infection-induced multi-organ damage (13), coagulopathy (14), mortality (15, 16), as well as attenuates the risk and severity of COVID-19 (17). Therefore it has been postulated that daily supplementation with moderate doses of vitamin D3 is a safe treatment for COVID-19 patients (18).

The mechanisms by which VD insufficiency exacerbates COVID-19-associated pneumonia remain poorly understood. However, most studies have focused on the pivotal roles of the VD/VD receptor (VDR) pathway in alleviating acute lung injury (ALI) and ARDS, a crucial component of the pathophysiological processes that occurred in almost 20% of the hospitalized patients (including ICU and non-ICU patients) with COVID-19 (19, 20). The two principal pathophysiological mechanisms involved in ARDS include the release of large amounts of pro-inflammatory cytokines and chemokines, known as a cytokine storm, and aberrant activation of the renin-angiotensin system (RAS) with a decrease of angiotensin-converting enzyme2 (ACE2) (21-23). Most previous work has revealed that the VD/VDR signaling axis may provide some beneficial effects in COVID-19 infection and especially in related ARDS phenotype through several mechanisms, such as attenuating the storm of cytokines and chemokines, modulating of the RAS, regulating the activity of a wide range of the immune cell types i.e., neutrophil and monocytes/macrophages, maintaining the integrity of the pulmonary epithelial barrier and stimulating epithelial repair, declining coagulation and thrombosis, and attenuating endothelial dysfunction (24-28).

VDR exerts its pleiotropic effects via binding with its active ligand, vitamin D, 1α,25-dihydroxy vitamin D3 [1,25(OH)2D3], and functions as a transcription factor (TF) on ~ 5% of human genes through binding to more than 23,000 cell-specific genomic locations, known as vitamin D response elements (VDREs)

(29, 30). The VDR gene is mapped at chromosome 12q13.11 which spans ~100 kb and has five promoters, eight coding exons, and six untranslated exons (31). Genetic variations in the VDR gene such as single nucleotide polymorphisms (SNPs) might influence the activity, stability, and expression levels of VDR products (mRNAs and/or proteins), subsequently altering the VD-VDR signaling axis, ultimately leading to disturbance of VD immune-regulatory functions. To date, a vast amount of investigations have been accomplished regarding the association of VDR polymorphisms with susceptibility to different diseases, including autoimmune disorders, cancers, viral and bacterial respiratory infections (32-35). Collectively, a few VDR gene variants that have been observed in relation to predisposing to various conditions with contradictory results include ApaI (rs7975232; intron 8; C>A), BsmI (rs1544410; intron 8; G>A), Tru9I (rs757343; intron 8; G>A), TaqI (rs731236; exon 9; A>G), BglI (rs739837; 3′UTR region; C>T), FokI (rs2228570; exon 2; C >T), CDX2 (rs11568820; promoter; G>A), and EcoRV or A-1012G/GATA (rs4516035; promoter; T>C). Hence, we aimed to evaluate the potential association of the aforementioned eight SNPs located in the 5′ end (FokI, CDX2, and EcoRV) and also 3′end (ApaI, BsmI, Tru9I, TaqI, and BglI) of the VDR gene with the severity of COVID-19 in an Iranian population. The identification of genetic variants linked with variable susceptibility of individuals to COVID-19 infection and severity of adverse complications could ultimately help open new avenues, including innovative personalized treatments, stratifying individuals according to the risk, and prioritization of subjects at greater risk for protection, assisting current biomedical research efforts to combat the virus, and also guide current genetics and genomics research towards candidate gene variants that warrant further investigation in larger studies.

Material and methods

COVID-19 patients

Five hundred COVID-19 patients were recruited in the current study that hospitalized at several different hospitals (Iran), during the period between May 5 and September 25, 2020. The COVID-19 diagnoses were established based on a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and/or pharyngeal swabs, following WHO interim guidance (36). The enrolled patients were categorized into 3 groups based on clinical manifestations: group I, 160 asymptomatic subjects, according to the absence of clinical symptoms and no need for hospitalization or ventilation; group II, 250 mild/moderate patients with a wide range of symptoms, including fever, sore throat, dry cough, headache, shortness of breath, diarrhea, myalgia, fatigue, nausea, vomiting, and parageusia; and group III, 90 subjects with a severe/critical condition. Regarding respiratory impairment, severe cases require non-invasive ventilation, while critical patients, defined as respiratory failure, requiring invasive ventilation and intensive care unit (ICU) admission. The presence of comorbidities (hypertension, diabetes, asthma, cardiovascular disease, chronic renal disease, and malignancy) was obtained from the participant's medical records (**Table 1**). The current research received approval from the national ethics committee and the study was conducted in agreement with the ethical principles of the Declaration of Helsinki. All the patients or their representatives gave their consent to participate.

VDR gene polymorphisms genotyping by PCR-RFLP

Peripheral blood was taken from each of the participants and DNA extraction was applied by High Pure PCR Template Preparation Kit (Roche Applied Science, USA) following the manufacturer's recommendations. The concentration and purity, as well as quality of DNA, were determined by NanoDropND-1000 Spectrometer (ThermoScientific, Boston, MA) and gel electrophoresis, respectively. The target SNPs were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Primers were designed using PRIMER3 online software (version 4.1.0) (https://primer3.ut.ee/) and their specificity was assessed using primer blast and possible secondary structures were analyzed using GENE RUNNER software (Gene Runner version 6.5.52). The primer sequences, PCR thermal profiles, expected amplicon size, and RFLP patterns are summarized in **Table 2**. It should be noted that in the present study, regardless of the type of substituted nucleotide(s) in SNP locations, the "capital" letter represents SNP-related major allele, and the small letter indicate minor allele. Accordingly, the major and minor alleles of ApaI [C and A (C>A), respectively] indicate as "A" and "a", BsmI alleles indicate as "B" and "b", Tru9I alleles indicate as "U" and "u", TaqI alleles indicate as "T" and "t", BglI alleles indicate as "G" and "g", FokI alleles indicate as "F" and "f", CDX2 alleles indicate as "C" and "c", and EcoRV alleles indicate as "E" and "e". It is expected that the restriction enzymes can digest PCR products of major alleles (capital letters) in SNPs ApaI, BsmI, BglI, CDX2, and EcoRV, and digest PCR products of minor alleles (small letters) in Tru9I, TaqI, and FokI. PCR reactions were carried out in a 25 µl reaction mixture containing 12.5 µl Taq DNA Polymerase 2x Master Mix (Amplicon, DENMARK), 1 µl of each primer (10 pmol), 1 µl genomic DNA (50 ng/ µl), and 9.5 µl d.d.H2O in a thermal cycler instrument (Applied Biosystems, GeneAmp 2720, Singapore) under the PCR parameters indicated in Table 2. The PCR products were examined by 1.5% agarose gel electrophoresis to ensure appropriate amplification. Subsequently, the amplified PCR products were digested with the corresponding restriction enzymes including ApaI, BsmI, MseI (isoschizomer of Tru9I enzyme), TaqI, BglI, FokI, HpyCH4III (used to genotyping CDX2), and EcoRV following the manufacturer's instructions. Digested products were then electrophoresed on 2-3% agarose gel and the genotypes of all the SNPs were determined based on digestion patterns.

Statistical analysis

All statistical analyses were implemented in the Statistical Package for the Social Sciences version 19 (IBM SPSS Inc, Chicago, IL, USA) and https://www.medcalc.org/calc/odds_ratio.php. The One-Sample Kolmogorov-Smirnov test was used to check the normal distribution of numerical variables. Student's unpaired t-tests and chi-square (χ^2) tests were used to compare quantitative clinical data and qualitative demographic data between paired-groups of COVID-19, including asymptomatic vs mild and moderate (I vs. II), asymptomatic vs. severe/critical (I vs. III), and mild/moderate vs severe/critical groups (II vs. III). Odds ratios (ORs) and their associated 95% confidence intervals (95% CIs) were calculated by https://www.medcalc.org/calc/odds_ratio.php, as a measure to show the strength of associations with three groups of COVID-19, demographic data, and clinical outcomes. In all statistical tests, P-values < 0.05 were considered to show statistically significant values.

Results

Baseline characteristics of patients

In our study, 500 COVID-19 patients were enrolled that were confirmed with a positive viral RT-PCR test, with an average age of 53.30 ± 16.16 years and 58.6% of them were men. The participants consisted of 32.0% asymptomatic patients (group I; average age 50.28 ± 16.76 years), 50.0% mild/moderate subjects (group II; average age 53.10 ± 16.10 years), and 18.0% severe/critical cases (group III; average age 59.19 ± 13.62 years). As presented in **Table 1**, no significant differences were found in sex ratio, defined as ($\frac{\text{No. of males}}{\text{No. of females}}$), among three groups (P = 0.161), as well as between the paired-groups I vs II, I vs III, and II vs III (P = 0.982, P = 0.090, and P = 0.069, respectively). However, we observed significant differences in the average age of participants among three groups (P < 0.001), and also in I than III and II vs. III, but not between groups I and II (I vs. II) (P < 0.001, P = 0.006, and P = 0.187, respectively). Significant differences were observed between groups II and III in some features, including shortness of breath, fatigue, and parageusia (P values < 0.001), but not in other variables, such as fever, sore throat, dry cough, headache, diarrhea, myalgia, nausea, and vomiting (P values > 0.05).

In the case of comorbidities, we observed significant differences among three groups and also paired-groups of I-II, I-III, and II-III for diabetes, chronic renal disease, and asthma. According to these conditions, we found negative associations with the severity of COVID-19 patients. Higher remarkable frequencies of diabetes were observed in group II against group I, as well as in group III against groups I + II. Similar to diabetes, our data showed higher frequencies of chronic renal disease in group II than group I, as well as in group III than group I and also group II. Additionally, significantly higher frequencies of asthma conditions were observed in group III compared to group II. Interestingly, we found a higher frequency of asthma disease in group I versus group II, and the hypertension was noticeably higher in group III compared to group I and group II, but not in group pair I-II (P = 0.117). Additionally, a higher frequency of malignancy was shown in group III than group II, but not in paired-groups I-II and I-III (P = 0.445 and P = 0.116, respectively). We did not found any significant differences between/or among patients' groups for the cardiovascular disorder (P values > 0.05).

VDR gene polymorphism genotype and allelic distribution in three various groups of COVID-19 patients

VDR gene polymorphisms were genotyped for all studied participants, and the resulted RFLP products were visualized by 2-3% agarose gel electrophoresis (**Fig. 1**). Distribution of genotypes with the respective allele frequencies and associations of the FokI, CDX2, and EcoRV or A-1012G/GATA, ApaI, BsmI, Tru9I, TaqI, BglI VDR polymorphisms were analyzed in COVID-19 patients consisting of three groups of asymptomatic (I), mild/moderate (II), severe/critical patients (III) (**Tables 3 and 4**).

As it is indicated in Table 3, significant differences were found between asymptomatic (I) and symptomatic (II + III) patients in the genotypic distribution of FokI SNP only in the recessive genetic model, in which wild-type allele ("F") is recessive against to mutant allele ("f"). Based on this genetic model, a significantly lower genotypic frequency of "FF vs. ff + Ff" (P = 0.037) was observed in symptomatic compared to asymptomatic cases. Furthermore, genotypic distributions of the FokI showed a remarkable discrepancy in severe/critical patients compared to asymptomatic cases in recessive and codominant. No significant discrepancies were observed between asymptomatic and mild/moderate patients, as well as between mild/moderate and severe/critical patients for none of the proposed genetic models. Similar to genotypes, remarkable differences were found for FokI allelic distribution between symptomatic and asymptomatic, as well as between severe/critical and asymptomatic COVID-19 subjects. No remarkable discrepancies were found between asymptomatic and mild/moderate groups, as well as mild/moderate and severe/critical patients.

The genotypic distributions of the second selected 5′-end's VDR gene polymorphism, CDX2, in three various groups of COVID-19 patients were indicated in **Table 3**. The allelic frequency of CDX2 polymorphism, which is known as "C" (Wild-type) and "c" (mutated), was different in asymptomatic, mild/moderate, and severe/critical patients. We observed significant discrepancies in CDX2 genotypic distribution between symptomatic (II + III) and asymptomatic (I) groups only in the recessive genetic model. Moreover, significant differences were showed in the distribution of CDX2 genotypes in severe/critical compared to asymptomatic cases in the dominant model, in the recessive model, and in the codominant model, however, the genotypic distribution of CDX2 was not significantly different in the overdominant model. CDX2 allelic distributions in three various types of COVID-19 patients demonstrated results similar to FokI. The CDX2 allele frequency was found to be higher in symptomatic patients (II + III) than asymptomatic patients. Moreover, the allelic frequency of CDX2 was revealed to be significantly different in group III than group I. No significant discrepancies were identified in allelic and genotypic distribution of CDX2 SNP between mild/moderate vs. asymptomatic, as well as mild/moderate vs. severe/critical groups [P values > 0.05].

EcoRV polymorphism was the last selected SNP located in the 5′-end of the VDR gene, which showed more complexity in allelic and genotypic distributions (**Table 3**). Significantly, EcoRV genotypes were differentially distributed between symptomatic group (II + III) and asymptomatic group in three genetic models, including recessive, overdominant, and codominant ("Ee vs. EE") genetic models ($P < 0.05$). Similarly, our results showed a significantly different EcoRV genotypic distribution in both severe/critical group and mild/moderate group against the asymptomatic group in recessive, overdominant, and codominant ("Ee vs. EE") models ($P < 0.05$). The EcoRV genotypic distribution showed significant deviation between severe/critical patients and mild/moderate patients in two genetic models, including overdominant and codominant ($P < 0.05$). Furthermore, our findings demonstrated the significant allelic distribution of the EcoRV SNP between whole paired groups, excluding in Group III vs. group II.

The first selected 3′-end VDR gene polymorphism to evaluate its association with COVID-19 patients' severity was ApaI. As it has been shown in **Table 4,** ApaI genotypic distributions were remarkably different between symptomatic group (II + III) and asymptomatic group in two genetic models, including overdominant and codominant ($P < 0.05$). Moreover, we observed significant differences in the distribution of ApaI genotypes in the severe/critical group than the mild/moderate group in the overdominant genetic model, as well as in the mild/moderate group compared to asymptomatic patients in recessive and overdominant genetic models. Amazingly, we did not find any significant discrepancies in ApaI genotypic distribution between severe/critical and asymptomatic groups in any of the proposed genetic models. Moreover, no significant differences were found in ApaI allelic distribution among three different types of COVID-19 ($P > 0.05$).

The genotypic distribution of BsmI, the second studied SNP located in the 3′-end's VDR gene, revealed remarkable discrepancies only in the severe/critical group compared to the mild/moderate group for two genetic models, including recessive and overdominant models, in which wild-type allele (B) is recessive against mutant allele (b) (**Table 4**). As presented in Table 4, BsmI genotypic distributions were not significantly different between other COVID-19 patients' groups, including groups II & III vs. group I, group III vs. group I, group II vs. group I (P > 0.05). We also didn't found remarkable discrepancies in BsmI allelic distribution between all paired groups, except between the severe/critical group and mild/moderate group (P < 0.05).

As it is shown in **Table 4,** the genotypic distributions of Tru9I, the third studied SNP located in the 3′ end's VDR gene, were not observed significantly different for any proposed genetic models, between three groups of COVID-19 patients, including symptomatic (II + III) and asymptomatic groups, severe/critical and asymptomatic groups, mild/moderate and asymptomatic groups, and eventually, severe/critical and mild/moderate groups (P > 0.05). Moreover, no significant discrepancies were found in Tru9I allelic distribution between paired groups, excluding in severe/critical group compared to mild/moderate group, in which lower rates of "U" vs. "u" and higher rates of "u" vs. "U" were significantly different between groups. TaqI polymorphism was another selected SNP in the present study that is located in the 3′ end's VDR gene. As is indicated in Table 4, our data didn't reveal any remarkable discrepancies in genotypic and allelic distributions of TaqI and BglI SNPs, for any recommended genetic models, between various groups of COVID-19 patients (P > 0.05).

Association of VDR gene polymorphisms with demographic and clinical features, and comorbidities of COVID-19 patients

We evaluate the potential association of selected VDR SNPs with various demographic and clinical features of patients, including gender, fever, sore throat, dry cough, headache, shortness of breath, diarrhea, myalgia, fatigue, nausea, vomiting, and parageusia (**Tables 5 and 6**). Additionally, the association of VDR gene polymorphisms with multifactorial diseases that are revealed to function as critical prognostic comorbidities including hypertension, diabetes, asthma, cardiovascular disease, chronic renal disease, and malignancy, were measured in three groups of COVID-19 patients (**Tables 5 and 6**). Our results didn't show any significant associations between studied VDR gene SNPs and the aforementioned demographic/clinical features as well as comorbidities in both asymptomatic and in the mild/moderate COVID-19 patients (P values > 0.05). However, regarding the comorbidities, we found significant associations of EcoRV and BsmI SNPs with diabetes and chronic renal disease, respectively (P < 0.001 and P = 0.010, respectively). However, no significant associations were observed between VDR polymorphisms and other comorbidities in mild/moderate patients (P values > 0.05).

As presented in **Table 7**, remarkable differences were detected in BsmI genotypic distribution between mild/moderate patients with a positive/negative history of chronic renal disease in three genetic models, including recessive, overdominant, and codominant (P < 0.05). Similarly, significant discrepancies were identified in both allelic and genotypic distributions of EcoRV between mild/moderate patients with a positive history of diabetes versus cases with no diabetes, in all suggested genetic models. Accordingly, declined ratios of "EE + Ee vs. ee", "EE + ee vs. Ee", and "E vs. e" were seen in group II cases with diabetes versus group II cases without diabetes.

Remarkable associations between VDR gene polymorphisms with more clinical variables and comorbidities were represented in group III of COCID-19 patients (**Tables 5 and 6**). Regarding the signs and symptoms, significant associations were found between ApaI and CDX2 SNPs with shortness of breath, and Tru9I SNP with vomiting ($P < 0.001$, $P = 0.022$, and $P = 0.031$, respectively). Our data showed a significant association of both ApaI genotypes and alleles with shortness of breath in all proposed genetic models except the dominant model (**Table 7**). Our results also revealed remarkable associations of CDX2 genotypes and alleles with shortness of breath in dominant and codominant genetic models (**Table 7**). It was shown that rates of "CC + Cc vs. cc" and "C vs. c" were higher in severe/critical patients with shortness of breath, while the frequency of "cc vs. CC + Cc", "cc vs. CC", and "c vs. C" were lower.

Additionally, significant associations were observed between VDR gene variants and more comorbidities in severe/critical COVID-19 patients, including ApaI and asthma ($P = 0.034$), BsmI and chronic renal disease ($P = 0.014$), FokI and hypertension ($P = 0.027$), CDX2 and both hypertension and diabetes ($P = 0.36$ and $P = 0.42$, respectively), EcoRV and diabetes ($P = 0.045$) (**Tables 5 and 6**). As presented in **Table 7**, a significant association was found between ApaI and asthma in severe/critical COVID-19 patients only in the dominant genetic model, in which diminished proportion of the "AA + Aa vs. aa" and elevated proportion of the "aa vs. AA + Aa" were disclosed. Regarding the BsmI SNP, significant associations were found with chronic renal disease in dominant and codominant genetic models. Accordingly, a higher amount of "bb vs. BB + Bb" and "bb vs. BB" were found in severe/critical patients with chronic renal disease than those didn't have this comorbidity, while "BB + Bb vs. bb" was lower. The association of FokI genotypic distribution with hypertension was significant in severe/critical patients in dominant and codominant genetic models. The data revealed a reduced rate of "FF + Ff vs. ff", but increased rates of the "ff vs. FF + Ff" and "ff vs. FF" in group III patients with hypertension compared to negative hypertension history (**Table 7**). The results of the present study showed a significant CDX2 genotypic discrepancies in severe/critical patients with hypertension in dominant and overdominant genetic models, as well as cases with diabetes in dominant and codominant models compared to negative cases for these comorbidities (**Table 7**). Significantly, higher frequency of "cc vs. CC + Cc" and "CC + cc vs. Cc" were observed in group III COVID-19 patients with hypertension than patients with negative history of hypertension, while the frequency of "CC + Cc vs. cc" and "Cc vs. CC + cc" were considered to be reduced. Additionally, the results showed significantly increased amounts of "cc vs. CC + Cc", "cc vs. CC", and "c vs. C", and decreased frequency of "CC + Cc vs. cc" and "C vs. c" in severe/critical COVID-19 patients with diabetes compared to patients without diabetes. Finally, we observed significant association of EcoRV with diabetes in severe/critical patients in recessive, overdominant, and codominant genetic models, in which higher proportions of "ee + Ee vs. EE", "Ee vs. EE + ee", and "Ee vs. EE" were found in group III patients with diabetes than negative diabetes cases, while proportions of the "EE vs. ee + Ee" and "EE + ee vs. Ee" were lower (**Table 7**).

To improve the validity of achieved results, we evaluate the potential association of selected VDR SNPs with signs/symptoms and with comorbidities in all symptomatic COVID-19 patients by combining whole data, regardless of the types of COVID-19 (N = 340 cases, N = 500 cases, respectively). As presented in **Table 8**, interesting associations of VDR SNPs with symptoms and comorbidities were found that are briefly mentioned: ApaI with fever and asthma ($P = 0.001$ and $P = 0.023$, respectively), BsmI with chronic renal disease ($P = 0.029$), Tru9I with shortness of breath and hypertension ($P = 0.040$ and $P = 0.003$, respectively), FokI with fever and hypertension ($P = 0.042$ and $P = 0.045$, respectively), CDX2 with headache, hypertension, and diabetes ($P = 0.019$, $P = 0.005$ and $P = 0.015$, respectively), and EcoRV with diabetes ($P < 0.001$).

As detailed in **Table 9**, the observed associations of genotypic and allelic VDR polymorphisms with signs, symptoms, and comorbidities of COVID-19 patients (regardless of the group of disease) strongly depend on the genetic models. For instance, significant associations of both allelic and genotypic distributions with the fever of COVID-19 patients were detected in recessive, overdominant, and codominant genetic models. Additionally, we found a remarkable association of ApaI genotypic distribution with asthma in dominant and overdominant genetic models, but not in recessive and overdominant models, as well as in allelic distribution. Similar to our finding in the earlier section, significant differences in the distribution of genotypes were revealed between COVID-19 patients with the chronic renal disease compared to negative cases only in dominant and overdominant genetic models. Accordingly, a higher frequency of "bb vs. BB + Bb" and "BB + bb vs. Bb" were found, while the frequency of "BB + Bb vs. bb" and "Bb vs. BB + bb" were decreased. Despite the no significant association of Tru9I polymorphism with clinical characteristics in various groups of COVID-19 patients, significant associations of Tru9I with shortness of breath in the combined population of COVID-19 patients were found in recessive, codominant, as well as allelic genetic models. According to **Table 9**, increased rates of "uu + Uu vs. UU", "Uu vs. UU", and "u vs. U", and decreased rates of "UU vs. uu + Uu" and "U vs. u" were seen in COVID-19 patients with shortness of breath versus those who didn't have this symptom. The higher frequency of FokI variant showed significant associations with fever and hypertension in dominant, codominant, and allelic models, but not in recessive and overdominant genetic models (**Table 9**).

Moreover, CDX2 polymorphism was disclosed to have significant associations with three clinical features, including headache, hypertension, and diabetes. In respect of headache and hypertension, significant differences were illustrated in the allelic distribution, as well as in the dominant and codominant models for genotypic distributions, but not in recessive and overdominant genetic models (**Table 9**). According to both headache and hypertension features, the results revealed elevated ratios of "cc vs. CC + Cc", "cc vs. CC", and "c vs. C", but decreased ratios of "CC + Cc vs. cc" and "C vs. c" in COVID-19 patients with these clinical features against to subjects without these variables. Furthermore, CDX2 was indicated to possess a strong association with diabetes in both allelic and all genetic models, except in the overdominant model in combined samples of COVID-19 patients (**Table 9**). Accordingly, higher rates of the "cc vs. CC + Cc", "cc + Cc vs. CC"." cc vs. CC", and "c vs. C" were recognized in COVID-19 patients with diabetes than patients without this comorbidity, nevertheless, lower rates of the " CC + Cc vs. cc", " CC vs. cc + Cc", and " C vs. c" were illustrated. The last finding was the association between EcoRV allelic and genotypic distribution and diabetes in all proposed genetic models (**Table 9**). Our results revealed increased rates of "ee vs. EE + Ee", "ee + Ee vs. EE", "Ee vs. EE + ee", "ee vs. EE", "Ee vs. EE", and "e vs. E", and decreased rates of the " EE + Ee vs. ee ", " EE vs. ee + Ee ", " EE + ee vs. Ee ", and " E vs. e " were seen in combined samples of COVID-19 subjects with diabetes compared to those with no diabetes.

Discussion

The wide spectrum of clinical manifestations of the resulting COVID-19 range from silent (asymptomatic) or mild symptoms of the upper respiratory tract such as familiar cold symptoms (fever, stuffy nose, cough, Sore throat, weakness) bronchitis to severe pneumonia with ARDS and death (37). Many Risk factors recognized for this coronavirus include advanced age, male gender, comorbidities, race, obesity, hypertension, diabetes, geographic region, and ethnicity (38). More importantly, several previous studies disclosed the association of specific human genetic variants with the predisposition of individuals to develop severe disease or susceptibility to infection (39-43). Some of the identified associations between genetic factors and different severity of COVID-19 or variable susceptibility to SARS-CoV-2 are ABO blood group, ACE2, APOE, HLA, IFITM3, TLR7, TMEM189-UBE2V1, TMPRSS2.

Mounting investigations have revealed the role of vitamin D deficiency as a pathogenic factor of COVID-19, leading to an increase in the predisposition and severity of individuals, especially via exacerbating acute lung injury and ARDS (44-46). Several types of research highlighted that patients with ARDS and also COVID-19 cases are even more vitamin D deficient than control subjects (47-50). Furthermore, more vitamin D deficiency [25(OH) D levels:< 50 nmol/L] and insufficiency [25(OH) D levels:50–75 nmol/L)] was demonstrated in regions highly affected by COVID-19, such as Iran (51, 52). Undoubtedly, a complex relationship can be proposed between vitamin D and COVID-19, in which many environmental and genetic factors are implicated. Among environmental factors, seasonal variation in sun exposure, geographic latitudes, air pollution, and darker skin influence vitamin D formation by sunlight in vitro (53). Intriguingly, In Chicago, more than half of COVID-19 cases and around 70% of COVID-19 deaths were observed in African-American individuals (54) who are at a greater risk for vitamin D deficiency (55). The actions of vitamin D are largely mediated by its intranuclear receptor, VDR, which is extensively distributed in respiratory epithelial cells and immune cells (B cell, T cell, macrophages, and monocytes). The expression and regulation of VDR itself are influenced by several mechanisms, including cell-type-specific transcription factors (TFs), auto-regulation by vitamin D, methylation of its primary promoter, and genetic variations (56). Genetic variations in the VDR gene such as SNPs might alter the function VD/VDR pathway in bronchial epithelium and immune-regulatory functions, which consequently influence the susceptibility to a large number of diverse conditions (32, 33, 57, 58) and possibly COVID-19.

In the present study, the association of eight SNPs in the VDR gene with the severity of COVID-19 patients was evaluated. Our data showed significant associations for some of the SNP-related alleles and/or genotypes in one or more genetic models. FokI polymorphism in the exon 2 at the 5' end of the VDR gene is referred to as start codon polymorphism (SCP), in which the presence of the "T" allele (the mutated "f" allele) results in the translation of a 3 amino acid longer VDR protein, while the "C" allele (the wild type "F" allele) produces shorter VDR protein that is associated with 1.7-fold increased transcriptional activity (59-62). In the FokI variant, results showed this SNP as a pinpointed associated factor with COVID-19; in which "f" (mutated) allele frequencies were intended to be higher in symptomatic and severe/critical patients compared with asymptomatic COVID-19 affected people. Hence, it can be suggested that the "f" allele, is positively associated with signs, symptoms, and possibly the severity of COVID-19 affected peoples. FokI genotypic distributions illustrated important results based on recessive and codominant genetic models in COVID-19 individuals, including the decreased vulnerability of "FF" genotype compared with combined "Ff + ff" genotypes, and increased susceptibility of "ff" patients versus "FF" affected subjects to represent signs, symptoms, and possibly more serious outcomes. However, there were no significant differences between "FF" and "Ff" patients for the clinical characteristics of COVID-19. The meta-analyses showed an association of FokI polymorphism with susceptibility to virus infection (63). This association could be contributed to the changes in TFIIB-VDR interaction, transcription efficiency, the effects of FokI polymorphism on immune cell behavior (64). Based on a meta-analysis by Laplana et al., FokI polymorphism was associated with viral infections, wherein the TT genotype and T allele were reported to be risk factors for infections with enveloped viruses, including RSV (65). In this line, the risk f-allele may have a lower transcription of VDR decreasing the efficiency of the vitamin D pathway by hampering the binding of vitamin D to VDR and affecting the expression of vitamin D responsive genes. Further, no significant differences were disclosed in FokI allelic and genotypic distributions between mild/moderate and asymptomatic groups, as well as between mild/moderate and severe/critical patients.

The Cdx-2 site in the 1a promoter region of the VDR gene is a functional binding site for the transcription factor Cdx-2. G to A substitution polymorphism at this site has been found to alter the transcription of the VDR gene, whereby the A-allele increases binding to the Cdx-2 protein and transcription activity of the VDR promoter compared with the G allele (66). According to the CDX2 results, "c" minor allele frequency was higher in symptomatic and severe/critical patients against asymptomatic COVID-19 cases, while "C" major allele rates were lower. Thus, the alleles "c" and "C" can be introduced as risk and protective factors, respectively, for signs, symptoms, and maybe the severity of the COVID-19. CDX2 genotypic distributions illustrated more interesting findings based on dominant, recessive, and codominant genetic models in COVID-19 patients, including protective effects of "CC" versus "Cc + cc", susceptible effects of "cc" versus both "CC + Cc" and "CC" to have clinical features and likely severity of the disease. Cdx2 is considered as a functional polymorphism of the VDR gene that has been demonstrated to impact the immune system alter the risk of contracting certain infectious illnesses (e.g., tuberculosis and rubella) (67, 68). Nevertheless, no substantial link has been established between this SNP and autoimmune disorders such as T1D, MS, vitiligo, or psoriasis (69-72). Although it is uncertain why the polymorphism is connected to illnesses like tuberculosis, numerous studies have connected this association to VDR methylation, vitamin D-mediated control of chemokine-positive T cells, and impact adaptive cytokine responses (67, 68, 73).

The EcoRV polymorphism (rs4516035), like CDX2, is found in the promoter region of the VDR gene and is thought to play a role in the anticancer immune response. EcoRV (5' to exon 1a) is a regulatory region SNPs that can affect VDR transcription via TF binding differences (74). In the presented study, EcoRV allelic and genotypic distributions unveiled several intriguing findings. Firstly, EcoRV minor allele "e" frequencies were remarkably inclined to increase in symptomatic, mild/moderate, and severe/critical patients compared to asymptomatic COVID-19 patients, while major allele "E" rates were decreased. Therefore, negative and positive associations of "E" and "e" alleles, respectively, with clinical outcomes of COVID-19 can be proposed. Nonetheless, no significant discrepancy was found in allelic frequencies between mild/moderate and severe/critical patients. Accordingly, genetic model-based genotypic distributions of EcoRV polymorphism highlighted the protective role of "EE" vs. "Ee + ee", vulnerable effects of "Ee" versus "EE + ee", and "Ee" versus "EE". Amazingly, we didn't found any significant differences in the distribution of "ee" and "EE" genotypes among different clinical groups. Furthermore, increased frequencies of "Ee" versus "EE + ee" and "Ee" versus "EE" in severe/critical compared to mild/moderate patients, obviously demonstrated the important role of heterozygous "Ee" in the severity of COVID-19 patients. It is previously reported that EcoRv is correlated with optimal bone density, cancer risk, diabetes, and susceptibility to HIV-1 infection (74, 75).

The ApaI (rs7975232) intronic variation is anticipated to impact splice site alterations, which may change VDR translation. This variation is common, as indicated by 734 and 16,751 homozygous mutants in the 1000G and ExAC databases, respectively (76). ApaI allelic frequencies, determined as major "A" and minor "a" alleles, didn't show significant differences between various paired groups of COVID-19. The present study highlighted that the "AA" genotype made COVID-19 affected people more prone to possess signs and symptoms versus both "Aa + aa" and "Aa" genotypes based on paired-groups of the symptomatic-asymptomatic and mild/moderate-asymptomatic comparisons. Additionally, heterozygous "Aa" patients were more protected to show signs and symptoms compared to combined "AA + aa" genotypes. This finding was interestingly opposite between severe/critical and mild/moderate groups, in which a rising risk of severity was demonstrated in patients with "Aa" genotype compared to "AA + aa" genotypes. This could be explained by the involvement of several factors determining the severity of the disease and might not be directly related to ApaI effects. Association of ApaI with different conditions including cancers, type 1 diabetes, asthma, multiple sclerosis, and several autoimmune diseases has previously been reported (77, 78-80).

BsmI polymorphism was revealed not to have any significant differences in allelic and genotypic frequencies between asymptomatic COVID-19 patients and other groups, including mild/moderate, severe/critical, and also all symptomatic patients. However, remarkable discrepancies were observed in allelic and genotypic distributions between mild/moderate and severe/critical COVID-19 suffered individuals. Our finding disclosed that minor allele "b" acts as a predisposition factor to COVID-19 severity, but major allele "B" has a protective effect. Moreover, genetic model-based genotypic distributions illustrated that patients with the "BB" genotype versus combined "bb + Bb" genotypes have decreased risk to develop more serious forms of COVID-19. However, "Bb" symptomatic heterozygotes showed elevated vulnerability to have more seriously COVID-19 than combined "BB + Bb" genotypes. VDR has an essential function in regulating the immune system in macrophages, dendritic cells, neutrophils, B cells, natural killer (NK) cells, and T lymphocyte. Therefore, these findings could be interpreted that VDR BsmI polymorphism has a significant role in susceptibility to and in the progression of viral infections such as COVID-19.

The SNP Tru9I didn't show any significant differences in allelic distribution between paired-group comparisons, except between severe/critical and mild/moderate groups, in which major "U" and minor "u" alleles were described as protective and risk factors, respectively. Tru9I genotypic frequencies didn't exhibit any significant association with clinical manifestations and also severity COVID-19. TaqI and BglI variants-related allelic and genotypic frequencies showed no significant association with clinical manifestations and also severity of COVID-19 affected peoples based on any genetic models in the present study. TaqI is a synonymous mutation at codon 352 in exon 9 at the 3' end of the VDR gene, in which "T" and "t" alleles were identified as absent and presence of the restriction site, respectively. The TT genotype has been reported to be associated with lower circulating levels of active vitamin D3 (81-83). ApaI, BsmI, Tru9I, and BglI are located in intron 8 at the 3' end of the VDR gene, which are considered silent SNPs. These polymorphisms do not change the amino acid sequence of the encoded protein, however, they may affect gene expression through the regulation of mRNA stability or linkage disequilibrium with other SNPs affecting the susceptibility to diseases (84).

Evaluating the potential association of VDR gene SNPs with signs and symptoms of COVID-19 patients, especially respiratory complications, surely highlights the more detailed importance of these variants in the severity of the disease. Despite the significant associations of some VDR gene variants with signs and symptoms of mild/moderate COVID-19 patients, amazing findings were pinpointed in group III. Accordingly, we found a strong association between both allelic and genotypic distributions of ApaI and CDX2 SNPs with shortness of breath. Regarding the ApaI, we found that major "A" and minor allele "a" provide a protective and susceptible effect, respectively, in severe/critical patients. According, our findings disclosed that severe/critical COVID-19 patients with "Aa" genotype and then "aa" genotype are more at risk of shortness of breath than "AA" patients. The minor "c" and major "C" alleles of CDX2 were found to have positive and negative associations with symptomatic and severe/critical COVID-19 groups, respectively. Moreover, negative association of "CC" genotype versus combined "Cc + cc" genotypes, positive associations of "cc" genotype versus both combined "CC + Cc" genotypes, and "CC" genotype to have clinical features and likely severity of disease are suggested. Nevertheless, "cc" versus both combined "CC + Cc" genotypes and "CC" genotype revealed a strong protective effect against shortness of breath. Unfortunately, we can't provide a rational explanation for these contradictory findings, therefore, it needs to be re-evaluated in other studies with larger sample sizes, in other ethnicities, and geographical regions.

Despite the high prevalence of conflicting results in previous investigations, we separately assessed the potential association of these VDR gene SNPs with some comorbidities including hypertension, diabetes, asthma, cardiovascular disease, chronic renal disease, and malignancy in various COVID-19 groups to further clarify how these genetic variants affect the prognosis of COVID-19 patients. No significant association was found between VDR gene variants and comorbidities in the asymptomatic COVID-19 group, while a strong association of VDR gene SNPs was seen with some of these conditions in mild/moderate and severe/critical groups.

Our results revealed that mild/moderate COVID-19 patients with the "BB" genotype are more prone to chronic renal disease, while patients with "Bb" are more protective. Therefore, it can be proposed that homozygotes subjects ("BB" and "bb") are at increased risk of chronic renal disease than heterozygotes in mild/moderate patients. Unlikely, we found an increased risk of the "bb" genotype versus the combined "BB + Bb" and "BB" genotype, and no significant discrepancy was observed between the distribution of the "Bb" and "BB" to have chronic renal disease in severe/critical COVID-19 patients. Consequently, we can suggest that the "Bb" genotype provides a protective role to have chronic renal disease in both mild/moderate and severe/critical COVID-19 patients, but the effects of "BB" and "bb" genotypes entirely depend on the stage of the disease. Regarding the EcoRV variant and diabetes in mild/moderate COVID-19 patients, we observed a negative association of the "E" allele and a positive association of the "e" allele. Also, our data revealed the protective effect of the "EE" genotype, but predisposing impacts of "ee" genotype, as well as increased risk of "Ee" genotype versus combined "EE + ee" and "EE" genotypes against diabetes. Therefore, it can be proposed that mild/moderate COVID-19 patients with 0, 1, and 2 alleles of minor allele "e" have a low, intermediate, and high risk of diabetes, respectively. Similar findings were observed in severe/critical patients, however, the distribution of "EE" and "ee" didn't show any remarkable difference. Overall, it can be argued that how the EcoRV variant is associated with diabetes depends entirely on the stage of COVID-19 disease, wherein the additive and overdominant genetic model better explains the observed findings in mild/ moderate and severe/critical groups, respectively.

In addition to EcoRV, CDX2 polymorphism has also been disclosed to have a significant association with diabetes in severe/critical COVID-19 patients. The major "C" and minor "c" alleles exhibited a negative and positive association with diabetes, respectively. Moreover, it was demonstrated that severe/critical patients with the "cc" genotype are more susceptible to have diabetes. Also, the CDX2 was recognized to have an association with hypertension, in which severe/critical COVID-19 patients with genotype "cc" have an increased risk for hypertension. Collectively, it can be proposed that the "cc" genotype causes an increased risk on severe/critical COVID-19 to exhibit both diabetes and hypertension comorbidities.

Similarly, FokI SNP illustrated a remarkable association with hypertension in severe/critical COVID-19 patients, in which elevated risk of hypertension was detected in "ff" genotype. ApaI genotypes were deciphered to possess a significant association with asthma, in which severe/critical COVID-19 patients with "aa" genotype strongly have increased risk than "AA + Aa" patients. Briefly, our data highlighted that ApaI SNP is associated with respiratory complications, including shortness of breath and asthma in severe/critical COVID-19 patients more likely based on overdominant and dominant genetic models, respectively.

To evaluate the reproducibility of the results and increase the accuracy of the study, the association of VDR gene SNPs with clinical outcomes and comorbidities was examined, regardless of the severity grouping of COVID-19 patients that in turn led to obtaining a larger sample size. Here, we found a significant association of VDR gene polymorphisms with several clinical outcomes of COVID-19 patients, including the association of ApaI and FokI variants with fever, Tru9I with shortness of breath, and CDX2 with the headache. By comparing these findings with the results described earlier, it is clear that these associations are quietly different. ApaI allelic and genotypic frequencies revealed that alleles "A" and "a" contribute to decreased and increased susceptibility of COVID-19 patients to fever, respectively. Our data revealed that patients with genotype "AA", are more protected to exhibit fever than "Aa + aa" patients, but the "Aa" patients are more susceptible to exhibit fever than "AA + aa", "AA" and "aa" genotypes. All of these findings pinpointed that the overdominant genetic model is the most likely model, in which an increased chance to have a fever might be occurred in heterozygotes compared to both dominant and recessive homozygotes. In respect of FokI SNP, we found that the major "F" allele associate with diminished susceptibility to fever, however the minor "f" allele associate with increased risk. Accordingly, we demonstrated that COVID-19 patients with the "ff" genotype have a higher chance to exhibit fever than "FF + Ff", "FF", and "Ff" patients. We didn't find a significant difference in the distribution of "FF" and "Ff" genotypes between patients with positive and negative fever histories. Consequently, the dominant genetic model is the most likely model, in which "ff" homozygotes are more vulnerable to fever than "Ff" heterozygotes and "FF" homozygotes. Our results disclosed that Tru9I major "U" and minor "u" alleles possess protective and predisposing effects to the shortness of breath, respectively. Further, "UU" COVID-19 patients are more protective to shortness of breath than "Uu + uu", while "Uu" patients are more susceptible to this respiratory complication than COVID-19 subjects with "UU" or "uu" genotypes. Consequently, although no significant difference between "Uu" and combined "UU + uu" was detected, we can propose an overdominant genetic model for this SNP, in which the heterozygotes "Uu" are at elevated risk compared to both "UU" and "uu" homozygotes. The findings of the present study identified the association of CDX2 allelic and genotypic association with headache. It was highlighted that the "C" major allele was negatively associated with headache, but the "c" minor allele was positively associated in COVID-19 patients. Accordingly, we found an increased risk of headache in COVID-19 subjects with "cc" genotype than combined "CC + Cc", "Cc", and "CC" genotypes. However, any significant differences in the distribution of "CC" and "Cc" genotypes didn't observe between COVID-19 cases with and without headache though.

The results of VDR gene SNPs association with comorbidities in the combined COVID-19 patient samples regardless of severity groups (N = 500 cases) were interestingly almost consistent with associations found in COVID-19 subgroups. ApaI was identified to associate with asthma in the dominant genetic model, in which COVID-19 patients with the "aa" genotype were at higher risk than "AA + Aa" to have asthma. The "bb" homozygotes of BsmI SNP were more susceptible to chronic renal disease in the combined samples (consists of 500 cases) and severe/critical subgroup, while both "BB" and "bb" genotypes increase the risk of chronic renal disease in mild/moderate group. The association of EcoRV polymorphism with diabetes was disclosed in combined COVID-19 samples and the most likely of proposed genetic models is additive genetic model, similar to mild/moderate group, in which the COVID-19 affected individuals with 0, 1, and 2 alleles of minor allele "e" are at low, intermediate, and high risk of diabetes, respectively, nonetheless, the overdominant model works better in the severe/critical group. Similar to the severe/critical class of COVID-19, we found a significant association of the CDX2 allelic and genotypic distributions with diabetes and hypertension, in which major "C" and minor "c" alleles exhibited a negative and positive association with both diabetes and hypertension, respectively. According to the results, the strongest genetic model is the dominant model, in which COVID-19 patients with the "cc" genotype have an increased risk of both diabetes and hypertension comorbidities compared to "CC + Cc", "CC", and "Cc" genotypes. Moreover, we found that FokI's major "F" and minor "f" alleles showed protective and susceptible effects on hypertension in combined COVID-19 samples, respectively. Similar to severe/critical patients, COVID-19 patients with "ff" genotype have elevated risk to hypertension versus "FF + Ff", "Ff", and "FF" genotypes. The last detected association between VDR gene variants and comorbidities was an association of Tru9I with hypertension, which was not observed in subtypes of COVID-19 patients. The results disclosed major "U" and minor "u" alleles as susceptible and protective factors for hypertension, respectively. Tru9I genotypic distributions suggested an overdominant genetic model as the most likely model, in which COVID-19 patients with "Uu" genotype had increased risk to hypertension than "UU + uu", "UU", "uu" patients.

To appropriately recognize individuals who may require hospital and/or ICU admission, risk stratification based on clinical, radiographic, and laboratory data appears to be essential. The existence of comorbidities is among the most alarming clinical characteristics. Some underlying illnesses such as hypertension, diabetes, lung disease, cardiovascular disease, age may be health issues for severe COVID-19 patients who have poorer outcomes than non-severe COVID-19 patients (85). Current evidence from the present study suggests that comorbidities including age, hypertension, diabetes, and chronic renal disease may work as a risk for the worst prognosis of COVID-19 patients. Consistent with previously reported data, our results revealed that severe/critical patients were older than mild/moderate and asymptomatic patients (86). Therefore, a positive association between elder ages and more severity of COVID-19 patients could be proposed. We observed greater frequencies of these diseases in severe/critical patients versus mild/moderate and asymptomatic patients, which is consistent with several reports (87-89). Asthma has been considered as a risk factor that makes people susceptible to more severe COVID-19 illness (90). However, managing COVID-19 in severe asthma is difficult, and it's uncertain if individuals with severe asthma are at a higher risk of having the poorest results, at least partially due to safety concerns about biologics and systemic corticosteroids (SCSs) (91). Our results showed an increased frequency of asthma conditions in severe/critical patients versus mild/moderate patients. Interestingly, a lower frequency of this condition was observed in mild/moderate patients than asymptomatic COVID-19 cases. Similar to our results, many recent studies revealed the strong positive association of cancer with the severity of COVID-19, even though inconsistent findings were also observed (92). Intriguingly, our results didn't show any significant discrepancies of cancer frequency between severe/critical and asymptomatic COVID-19 patients. Despite early studies suggested that cancer might be a separate risk factor for severe COVID-19, recent matched researches comparing outcomes between hospitalized cancer patients and matched controls found no statistically significant differences in death (93, 94). As a result, a history of cancer and cancer-directed treatments might not even be associated with a greater risk of the most serious COVID-19 outcomes in hospitalized individuals. A proinflammatory state and a weakened innate immune response are suggested as the common characteristics between these chronic illnesses and infectious diseases, which may be connected etiologically to its pathogenesis. More importantly, the co-existence of multiple comorbidities in patients seems to increase the risk of severity or death in COVID-19 disease. Regarding the signs and symptoms in symptomatic patients, increased significant frequencies of the shortness of breath, fatigue, and parageusia were illustrated in the severe/critical group compared to the mild/moderate group, which is similar to previous investigations (95). Breathlessness is a distressing and common symptom in patients with severe illness, and it is thought to be caused by physiological and structural abnormalities in the lungs. The increased ventilatory drive may rationalize our findings since individuals with moderate COVID-19 nevertheless respond physiologically to hypoxia.

Conclusion

Vitamin D has been shown to regulate macrophage responses, stopping them from producing excessive amounts of inflammatory cytokines and chemokines, which are common in COVID-19. Therefore, the prevalence and mortality rate of COVID-19 may depend on the modulatory effect of bioavailable Vitamin D levels of individuals, which is determined by the genetic background, such as VDR gene polymorphisms. Therefore, we designed the present study to explore the association of eight VDR gene SNPs with the clinical status and prognosis of COVID-19 patients. We found significant associations of VDR gene variants with several clinical outcomes such as severity and shortness of breath in mild/moderate and severe/critical cases of COVID-19. Nevertheless, the VDR gene SNPs could not be proposed as either independent or dependent risk factors to COVID-19-co-existing conditions, including hypertension, diabetes, asthma, cardiovascular disease, chronic renal disease, and malignancy. Our data showed that some VDR SNPs have a clinical impact on the COVID-19 patients and might be helpful to identify the individuals at high risk of COVID-19 severity in the Iranian population. Moreover, the variations in the prevalence of COVID-19 and its mortality rates among countries may be explained by vitamin D function differed by the VDR polymorphisms. However, the present study is preliminary with partially limited sample size. Thus, further experiments are suggested to identify the role of VDR polymorphisms as the cause-effect of COVID-19 severity in a larger population, in other ethnicities and geographical regions.

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CRediT Author contributions:

Asaad Azarnezhad and **Rasoul Abdollahzadeh:** Conceptualization, Methodology, Funding acquisition, and Project Administration. **Mohammad Hossein Shushizadeh, Rasoul Abdollahzadeh**, and **Asaad Azarnezhad**: Data curation, Data Interpretation, and Writing- Original draft preparation. **Mina Barazandehrokh** and **Sepideh Choopani**: Data curation, Visualization, Investigation, Reviewing and Editing, and Software, **Sahereh Paknahad, Maryam Pirhoushiaran, S.Zahra Makani, Razieh,** and **Zarifian Yeganeh:** Data curation, Data Interpretation, Laboratory works, revising and English grammar editing.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Fig. 1. The PCR-RFLP patterns of eight selected VDR polymorphisms. (**A**) Genotypes were determined from lanes 1–12 for ApaI, BsmI, FokI, and TaqI polymorphisms; (**B**) Genotyping results for BgII, HpyCH4III, Tru9I/Msel, and EcorVI polymorphisms. The RFLP product sizes for each genotype of the selected SNPs are indicated in Table 2.

Table 1. Baseline features of COVID-19 participants

variables	status		Asymptomatic patients (group I)	mild/ moderate illness (group II)	severe and critical illness (group III)	P- value (I and II)	P- value (I and III)	P- value (II and III)	Overall P- value
Number (%)	500 (100.0)		160 (32.0)	250 (50.0)	90 (18.0)				
Age (mean ± Std. Deviation)	53.30 ± 16.16		50.28 ± 16.76	53.10 ± 16.10	59.19 ± 13.62	0.187	**< 0.001**	**0.006**	**< 0.001**
Gender	Male	293 (58.60)	90 (56.3)	142 (56.8)	61 (67.8)	0.988	0.090	0.069	0.161
	Female	207 (41.40)	70 (43.7)	108 (43.2)	29 (32.2)				

Signs and symptoms

variables	status	Asymptomatic patients (group I)	mild/ moderate illness (group II)	severe and critical illness (group III)	P- value (II and III)
Fever	Yes	0 (0.0)	141 (56.4)	52 (57.8)	0.821
	No	160 (100.0)	109 (43.6)	38 (42.2)	
Sore throat	Yes	0 (0.0)	82 (32.8)	26 (28.9)	0.494
	No	160 (100.0)	168 (67.2)	64 (71.1)	
Dry cough	Yes	0 (0.0)	144 (57.6)	44 (48.9)	0.154
	No	160 (100.0)	106 (42.4)	46 (51.1)	
Headache	Yes	0 (0.0)	49 (19.6)	10 (11.1)	0.068
	No	160 (100.0)	201 (80.4)	80 (88.9)	

Shortness of breath	Yes	0 (0.0)	32 (12.8)	58 (64.4)	**< 0.001**
	No	160 (100.0)	218 (87.2)	32 (35.6)	
Diarrhea	Yes	0 (0.0)	19 (7.6)	11 (12.2)	0.185
	No	160 (100.0)	231 (92.4)	79 (87.8)	
Myalgia	Yes	0 (0.0)	62 (24.8)	17 (18.9)	0.255
	No	160 (100.0)	188 (75.2)	73 (81.1)	
Fatigue	Yes	0 (0.0)	26 (10.4)	31 (34.4)	**< 0.001**
	No	160 (100.0)	224 (89.6)	59 (56.6)	
Nausea	Yes	0 (0.0)	24 (9.6)	15 (16.7)	0.071
	No	160 (100.0)	226 (90.4)	75 (83.3)	
Vomiting	Yes	0 (0.0)	18 (7.2)	11 (12.2)	0.144
	No	160 (100.0)	232 (92.8)	79 (87.8)	
Parageusia	Yes	0 (0.0)	12 (4.8)	26 (28.9)	**< 0.001**
	No	160 (100.0)	238 (95.2)	64 (71.1)	

Comorbidities

variables	status	Asymptomatic patients (group I)	mild/ moderate illness (group II)	severe and critical illness (group III)	P- value (I and II)	P- value (I and III)	P- value (II and III)	Overall P- value
Hypertension	Yes	19 (11.9)	44 (17.6)	45 (50.0)	[illegible]	**< 0.001**	**< 0.001**	**< 0.001**
	No	141 (88.1)	206 (82.4)	45 (50.0)				
	OR (95% CI)$_{III\ vs.\ I}$ = 7.42 (3.94- 13.97), OR (95% CI)$_{III\ vs.\ II}$ = 4.68 (2.77- 7.92)							
Diabetes	Yes	16 (10.0)	44 (17.6)	32 (35.6)	**0.034**	**< 0.001**	**< 0.001**	**< 0.001**
	No	144 (90.0)	206 (82.4)	58 (64.4)				
	OR (95% CI)$_{II\ vs.\ I}$ = 1.92 (1.04- 3.54), OR (95% CI)$_{III\ vs.\ I}$ = 4.97 (2.53- 9.73), OR (95% CI)$_{III\ vs.\ II}$ = 2.58 (1.50- 4.44)							
Asthma	Yes	22 (13.8)	14 (5.6)	15 (16.7)	**0.002**	**< 0.001**	**0.001**	**< 0.001**
	No	138 (86.2)	236 (94.4)	75 (83.3)				
	OR (95% CI)$_{II\ vs.\ I}$ = 0.37 (0.18- 0.75), OR (95% CI)$_{III\ vs.\ II}$ = 3.3[illegible] (1.56- 7.31)							
Cardiovascular disease	Yes	18 (11.2)	24 (9.6)	11 (12.2)	0.591	0.818	0.483	0.746
	No	142 (88.8)	226 (90.4)	79 (87.8)				
Chronic renal disease	Yes	11 (6.9)	39 (15.6)	25 (27.8)	**0.008**	**< 0.001**	**0.011**	**< 0.001**
	No	149 (93.1)	211 (84.4)	65 (72.2)				
	OR (95% CI)$_{II\ vs.\ I}$ = 2.50 (1.24- 5.05), OR (95% CI)$_{III\ vs.\ I}$ = 5.21 (2.42- 11.22), OR (95% CI)$_{III\ vs.\ II}$ = 2.08 (1.17- 3.69)							
Malignancy	Yes	9 (5.6)	10 (4.0)	10 (11.1)	0.445	0.116	**0.014**	**0.046**
	No	151 (94.4)	240 (96.0)	80 (88.9)				
	OR (95% CI)$_{III\ vs.\ II}$ = 3.00 (1.21- 7.47)							

Table 2. Primers sequences, PCR thermocycling profile, amplicon size and RFLP pattern of different genotypes for the selected VDR gene polymorphisms.

SNP (RefSNPs)/ other names	restriction enzymes	Primer sequences and PCR thermal profiles	Amplicon (bp)	Restriction fragments (bp)
rs7975232	ApaI	**Forward: 5′CTGCCGTTGAGTGTCTGTGT3′**	242	C: 191 + 51
		Reverse: 5′TCGGCTAGCTTCTGGATCAT3′		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 58 °C for 30 s, and 72 °C for 30 s, and final extension: 72 °C for 7 min		A: 242
rs1544410	BsmI	**Forward: 5′GGGAGACGTAGCAAAAGGAG3′**	297	G: 192 + 105
		Reverse: 5′CCATCTCTCAGGCTCCAAAG3′		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 57 °C for 30 s, and 72 °C for 30 s, and final extension: 72 °C for 7 min		A: 297
rs739837	BglI	**Forward: 5′CACCCAGCCCATTCTCTCTC3′**	248	C: 178+ 70
		Reverse: 5′GCAGGTGTCTCTGTCCCTGA3′		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 62 °C for 30 s, and 72 °C for 30 s, and final extension: 72 °C for 7 min		T: 248
rs731236	TaqI	**Forward: 5′CCCATGAAGCTTAGGAGGAA3′**	699	T: 699
		Reverse: 5′TCATCTTGGCATAGAGCAGGT3′		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 60 °C for 30 s, and 72 °C for 50 s, and final extension: 72 °C for 10 min		C: 604 + 95
rs757343	Tru9I/ MseI	**Forward: 5′**CTTTGGAGCCTGAGAGATGG**3′**	235	G: 235
		Reverse: 5′CTCCAGTCCAGGAAAGCATC**3′**		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 59 °C for 30 s, and 72 °C for 30 s, and final extension: 72 °C for 7 min		A: 162 + 73
rs2228570	FokI	**Forward: 5′CTGGCACTGACTCTGGCTCT3′**	247	C: 247
		Reverse: 5′TGCTTCTTCTCCCTCCCTTT3′		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 62 °C for 30 s, and 72 °C for 30 s, and final extension: 72 °C for 7 min		T: 185 + 62
rs11568820/ CDX2	HpyCH4III	**Forward:: 5′**AGGAGGGAGGGAGGAAGG**3′**	414	G: 254 + 110 + 50
		Reverse: 5′TGAGAGACATGAGCGTGGAG**3′**		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 61 °C for 30 s, and 72 °C for 30 s, and final extension: 72 °C for 7 min		A: 254 + 160
rs4516035/ GATA/ A-1012G	EcoRV	**Forward: 5′**GAGGACAGGTGAAAAAGATGGGGTTC**3′**	181	T: 154 + 27
		Reverse: 5′CCTCCTCTGTAAGAGGCGAATAGCGAT**3′**		
		Initial denaturation: 95 °C for 5 min, 35 cycles: 95 °C for 30 s, 68 °C for 30 s, and 72 °C for		C: 181

		30 s, and final extension: 72 °C for 7 min		

Table 3. Allelic and genotypic comparison of selected polymorphisms in the 5'-end of VDR gene among three different groups of COVID-19 patients

FokI (rs2228570)			
Genotypes and Alleles	*Group I (%)*	*Group II (%)*	*Group III (%)*
FF (%)	*75 (46.88)*	*96 (38.40)*	*30 (34.44)*
Ff (%)	*66 (41.25)*	*116 (46.40)*	*42 (33.33)*
ff (%)	*19 (11.87)*	*38(15.20)*	*18 (32.23)*
F (%)	*216 (67.50)*	*308 (61.60)*	*102 (56.67)*
f (%)	*104 (32.50)*	*192 (38.40)*	*78 (43.33)*
HWE Chi-squared value (P- value)*	*0.57 (0.449)*	*0.09 (0.761)*	*0.22 (0.637)*

Odds ratio (95% CI) and P- values					
Genetic models		*Groups II & III vs. group I*	*Group III vs. group I*	*Group III vs. group II*	*Group II vs. group I*
Dominant	*FF + Ff vs. ff*	*0.68 (0.39- 1.19), P = 0.181*	*0.54 (0.27- 1.09), P = 0.086*	*0.72 (0.39- 1.34), P = 0.294*	*0.75 (0.42- 1.36), P = 0.344*
	ff vs. FF + Ff	*1.47 (0.84- 2.56), P = 0.181*	*1.85 (0.92- 3.70), P = 0.086*	*1.39 (0.75-2.56), P = 0.294*	*1.33 (0.39-2.38), P = 0.344*
Recessive	*ff + Ff vs. FF*	***1.50 (1.02- 2.19), P = 0.037***	***1.77 (1.03- 3.02), P = 0.038***	*1.2[illegible] ([illegible].75- 2.07), P = [illegible].394*	*1.42 (0.95- 2.12), P = 0.090*
	FF vs. ff + Ff	***0.67 (0.46- 0.98), P = 0.037***	***0.57 (0.33- 0.97), P = 0.038***	*0.[illegible] (0.4[illegible]- [illegible].33), P = [illegible].394*	*0.70 (0.47- 1.05), P = 0.090*
Overdominant	*Ff vs. FF + ff*	*1.24 (0.85- 1.81), P = 0.274*	*1.25 (0.74- 2.10), P = 0.407*	*1.[illegible]1 (0.[illegible]2- 1.64), P = 0.965*	*1.23 (0.83- 1.84), P = 0.306*
	ff + FF vs. Ff	*0.81 (0.55-1.18), P = 0.274*	*0.80 (0.85-1.82), P = 0.407*	*0.99 [illegible]0.61- 1.61),P = 0.965*	*0.81 (0.54- 1.21),P = 0.306*
Codominant	*ff vs. FF*	*1.75 (0.97- 3.18), P = 0.064*	***2.37 (1.10- 5.12), P = 0.028***	*[illegible].52 (0.76- 3.04), P = 0.241*	*1.56 (0.83- 2.93), P = 0.164*
	Ff vs. FF	*1.42 (0.95- 2.14), P = 0.087*	*1.59 (0.90- 2.82), P = [illegible].11[illegible]*	*1.16 (0.68- 1.99), P = 0.594*	*1.37 (0.90- 2.11), P = 0.146*
Allelic	*F vs. f*	***0.73 (0.55- 0.97), P = 0.028***	***0.63 (0.43- 0.92), P = 0.[illegible]***	*0.82 (0.58- 1.15), P = 0.246*	*0.77 (0.58- 1.04), P = 0.087*
	f vs. F	***1.37 (1.03- 1.82) , P = 0.028***	***1.59 (1.09- 2.[illegible]3), [illegible] = 0.016***	*1.22 (0.87- 1.72), P = 0.246*	*1.30 (0.96- 1.72), P = 0.087*

CDX2 (rs11568820)			
Genotypes and Alleles	*Group I*	*Group II*	*Group III*
CC (%)	*7[illegible] (45.[illegible]3)*	*95 (38.00)*	*28 (31.11)*
Cc (%)	*[illegible]2 (3[illegible].75)*	*110 (44.00)*	*37 (41.11)*
cc (%)	*25 ([illegible]5.62)*	*45 (18.00)*	*25 (27.78)*
C (%)	*208 (6[illegible].00)*	*300 (60.00)*	*93 (51.67)*
c (%)	*112 (35.00)*	*200 (40.00)*	*87 (48.33)*
HWE Chi-squared value (P- value)*	*3.[illegible]2 (0.061)*	*1.74 (0.188)*	*2.82 (0.093)*

Odds ratio (95% CI) and P- values					
Genetic models		*Groups II & III vs. group I*	*Group III vs. group I*	*Group III vs. group II*	*Group II vs. group I*
Dominant	*CC + Cc vs. cc*	*0.71 (0.43- 1.18), P [illegible] 0.1[illegible]8*	***0.48 (0.26- 0.90), P = 0.023***	*0.57 (0.33- 1.00), P = 0.051*	*0.84 (0.49- 1.44), P = 0.533*
	cc vs. CC + Cc	*1.40 (0.85- 2.3[illegible] P = 0.[illegible]88*	***2.08 (1.11- 3.85),P = 0.023***	*1.75 (1.00- 3.03), P = 0.051*	*1.19 (0.69- 2.04), P = 0.533*
Recessive	*cc + Cc vs. CC*	***1.48 (1.01- 2.1[illegible] P = 0.044***	***1.86 (1.08- 3.20), P = 0.026***	*1.36 (0.81- 2.27), P = 0.244*	*1.37 (0.92- 2.05), P = 0.126*
	CC vs. cc + Cc	***0.68 ([illegible]- 0.[illegible]), P = 0.044***	***0.54 (0.31- 0.93) , P = 0.026***	*0.74 (0.44- 1.24), P = 0.244*	*0.73 (0.49- 1.09), P = 0.126*
Overdominant	*Cc vs. CC + cc*	*[illegible].20 ([illegible].82- [illegible].77), P = 0.343*	*1.10 (0.65- 1.87), P = 0.714*	*0.89 (0.55- 1.45), P = 0.635*	*1.24 (0.83- 1.86), P = 0.294*
	CC + cc vs. Cc	*0.83 ([illegible].57- 1.22), P = 0.343*	*0.91 (0.54- 1.54), P = 0.714*	*1.12 (0.69- 1.82), P = 0.635*	*0.81 (0.54- 1.21), P = 0.294*
Codominant	*cc vs. CC*	*1.67 (0.97- 2.86), P = 0.066*	***2.63 (1.28- 5.26), P = 0.008***	*1.89 (0.99- 3.57), P = 0.054*	*1.39 (0.78- 2.44), P = 0.270*
	Cc vs. CC	*1.41 (0.93- 2.13), P = 0.106*	*1.56 (0.86- 2.83), P = 0.146*	*1.14 (0.65- 2.00), P = 0.645*	*1.36 (0.88- 2.11), P = 0.163*
Allelic	*C vs. c*	***0.74 (0.56- 0.97), P = 0.030***	***0.58 (0.40- 0.84), P = 0.004***	*0.71 (0.51- 1.00), P = 0.053*	*0.81 (0.60- 1.08), P = 0.151*
	c vs. C	***1.35 (1.03- 1.79), P = 0.030***	***1.72 (1.19- 2.50), P = 0.004***	*1.41 (1.00- 1.96), P = 0.053*	*1.24 (0.93- 1.67), P = 0.151*

EcoRV (rs4516035)			
Genotypes and Alleles	*Group I*	*Group II*	*Group III*
EE (%)	*107 (66.88)*	*134 (53.60)*	*39 (43.33)*
Ee (%)	*43 (26.87)*	*95 (38.00)*	*46 (51.11)*
ee (%)	*10 (6.25)*	*21 (8.40)*	*5 (2.56)*
E (%)	*257 (80.31)*	*363 (72.60)*	*124 (68.89)*
e (%)	*63 (19.69)*	*137 (27.40)*	*56 (31.11)*
HWE Chi-squared value (P- value)*	*3.61 (0.058)*	*0.50 (0.478)*	*3.332 (0.068)*

Odds ratio (95% CI) and P- values					
Genetic models		*Groups II & III vs. group I*	*Group III vs. group I*	*Group III vs. group II*	*Group II vs. group I*
Dominant	*EE + Ee vs. ee*	*0.81 (0.38-1.71), P = 0.574*	*1.13 (0.38- 3.43), P = 0.823*	*1.56 (0.57- 4.27), P = 0.387*	*0.73 (0.33- 1.59), P = 0.423*
	ee vs. EE + Ee	*1.24 (0.59- 2.63), P = 0.574*	*0.89 (0.29- 2.63), P = 0.823*	*0.64 (0.23- 1.75), P =*	*1.37 (0.63- 3.00), P =*

				0.387	0.423
Recessive	ee + Ee vs. EE	**1.95 (1.32- 2.88), P < 0.001**	**2.64 (1.55- 4.49), P < 0.001**	1.51 (0.93- 2.46), P = 0.096	**1.75 (1.16- 2.64), P = 0.008**
	EE vs. ee + Ee	**0.51 (0.35- 0.76), P < 0.001**	**0.38 (0.22- 0.65), P < 0.001**	0.66 (0.41- 1.08), P = 0.096	**0.57 (0.38- 0.86), P = 0.008**
Overdominant	Ee vs. EE + ee	**1.93 (1.28- 2.91), P = 0.002**	**2.85 (1.66- 4.89), P < 0.001**	**1.71 (1.05- 2.77), P = 0.031**	**1.67 (1.08- 2.57), P = 0.021**
	EE + ee vs. Ee	**0.52 (0.34- 0.78), P = 0.002**	**0.35 (0.21- 0.60), P < 0.001**	**0.59 (0.36- 0.95), P = 0.031**	**0.60 (0.39- 0.93), P = 0.021**
Codominant	ee vs. EE	1.61 (0.75- 3.47), P = 0.226	1.37 (0.44- 4.27), P = 0.585	0.82 (0.29- 2.31), P = 0.705	1.68 (0.76- 3.71), P = 0.202
	Ee vs. EE	**2.03 (1.34- 3.08), P < 0.001**	**2.94 (1.69- 5.11) , P < 0.001**	**1.66 (1.01- 2.75), P = 0.047**	**1.76 (1.14- 2.74), P = 0.012**
Allelic	E vs. e	**0.62 (0.45- 0.85), P = 0.004**	**0.54 (0.36- 0.83), P = 0.004**	0.84 (0.58- 1.21), P = 0.344	**0.65 (0.46- 0.91), P = 0.013**
	e vs. E	**1.61 (1.18- 2.22), P = 0.004**	**1.85 (1.21- 2.78), P = 0.004**	1.19 (0.83- 1.72), P = 0.344	**1.54 (1.10- 2.17), P = 0.013**

Table 4. Allelic and genotypic comparison of 3′ end's VDR polymorphisms among three different groups of COVID-19 patients

ApaI (rs7975232)			
Genotypes and Alleles	*Group I (%)*	*Group II (%)*	*Group III (%)*
AA (%)	*51 (31.88)*	*107 (42.80)*	*31 (34.44)*
Aa (%)	*88 (55.00)*	*103 (41.20)*	*50 (55.56)*
aa (%)	*21 (13.12)*	*40 (16.00)*	*9 (10.00)*
A (%)	*190 (59.38)*	*317 (63.40)*	*112 (62.22)*
a (%)	*130 (40.62)*	*183 (36.60)*	*68 (37.78)*
HWE Chi-squared value (P- value)*	*3.14 (0.076)*	*3.15 (0.076)*	*2.97 (0.085)*

Odds ratio (95% CI) and P- values

Genetic models		*Groups II & III vs. group I*	*Group III vs. group I*	*Group III vs. group II*	*Group II vs. group I*
Dominant	*AA + Aa vs. aa*	*0.90 (0.52- 1.56), P = 0.699*	*1.36 (0.59- 3.11), P = 0.467*	*1.71 (0.80- 3.69), P = 0.169*	*0.79 (0.45- 1.40), P = 0.426*
	aa vs. AA + Aa	*1.11 (0.64- 1.92), P = 0.699*	*0.74 (0.32- 1.70), P = 0.467*	*0.59 (0.27- 1.25), P = 0.169*	*1.27 (0.71- 2.22), P = 0.426*
Recessive	*aa + Aa vs. AA*	*0.69 (0.46- 1.02), P = 0.062*	*0.89 (0.52- 1.54), P = 0.678*	*1.42 (0.86- 2.35), P = 0.167*	***0.63 (0.41- 0.95), P = 0.027***
	AA vs. aa + Aa	*1.45 (0.98- 2.17), P = 0.062*	*1.12 (0.65- 1.92), P = 0.678*	*0.70 (0.43- 1.16), P = 0.167*	***1.59 (1.05- 2.44), P = 0.027***
Overdominant	*Aa vs. AA + aa*	***0.67 (0.46- 0.98), P = 0.037***	*1.02 (0.61- 1.72), P = 0.932*	***1.78 (1.10- 2.90), P = 0.020***	***0.57 (0.38- 0.86), P = 0.007***
	AA + aa vs. Aa	***1.49 (1.02- 2.17), P = 0.037***	*0.98 (0.58- 1.64), P = 0.932*	***0.56 (0.35- 0.91), P = 0.020***	***1.75 (1.16- 2.63), P = 0.007***
Codominant	*aa vs. AA*	*0.86 (0.47- 1.58), P = 0.631*	*0.71 (0.29- 1.73), P = 0.446*	*0.78 (0.34- 1.77), P = 0.549*	*0.91 (0.49- 1.70), P = 0.762*
	Aa vs. AA	***0.64 (0.42- 0.97), P = 0.037***	*0.94 (0.53- 1.65), P = 0.815*	*1.68 (0.99- 2.83), P = 0.053*	***0.56 (0.36- 0.87), P = 0.009***
Allelic	*A vs. a*	*1.17 (0.89- 1.54), P = 0.260*	*1.13 (0.78- 1.64), P = 0.532*	*0.95 (0.67- 1.35), P = 0.779*	*1.19 (0.89- 1.58), P = 0.247*
	a vs. A	*0.86 (0.65- 1.12), P = 0.260*	*0.89 (0.61- 1.28), P = 0.532*	*1.05 (0.74- 1.49), P = 0.779*	*0.84 (0.63- 1.12), P = 0.247*

BsmI (rs1544410)			
Genotypes and Alleles	Group I	*Group II*	*Group III*
BB (%)	*63 (39.38)*	*112 (44.80)*	*29 (32.22)*
Bb (%)	*82 (51.25)*	*119 (47.60)*	*50 (55.56)*
bb (%)	*15 (9.37)*	*19 (7.60)*	*11 (12.22)*
B (%)	*208 (65.00)*	*343 (68.60)*	*108 (60.00)*
b (%)	*112 (35.00)*	*157 (31.40)*	*72 (40.00)*
HWE Chi-squared value (P- value)*	2.56 (0.110)	*2.75 (0.097)*	2.23 (0.135)

Odds ratio (95% CI) and P- values

Genetic models		*Groups II & III vs. group I*	*Group III vs. group I*	*Group III vs. group II*	*Group II vs. group I*
Dominant	*BB + Bb vs. bb*	*1.07 (0.56- 2.05), P = 0.841*	*0.74 (0.33- 1.70), P = 0.480*	*0.59 (0.27- 1.30), P = 0.189*	*1.26 (0.62- 2.55), P = 0.526*
	bb vs. BB + Bb	*0.94 (0.49- 1.79), P = 0.841*	*1.35 (0.59- 3.00), P = 0.480*	*1.70 (0.77- 3.70), P = 0.189*	*0.79 (0.39- 1.61), P = 0.526*
Recessive	*bb + Bb vs. BB*	*0.92 (0.63- 1.35), P = 0.657*	*1.37 (0.79- 2.35), P = 0.261*	***1.71 (1.03- 2.84), P = 0.039***	*1.38 (0.94- 2.04), P = 0.104*
	BB vs. bb + Bb	*1.09 (0.74- 1.59), P = 0.657*	*0.73 (0.43- 1.27), P = 0.261*	***0.59 (0.35- 0.97), P = 0.039***	*0.73 (0.49- 1.06), P = 0.104*
Overdominant	*Bb vs. BB + bb*	*0.94 (0.65- 1.37), P = 0.747*	*1.19 (0.71- 2.00), P = 0.513*	***2.43 (1.52- 3.89), P < 0.001***	*0.86 (0.58- 1.29), P = 0.471*
	BB + bb vs. Bb	*1.06 (0.73- 1.54), P = 0.747*	*0.84 (0.50- 1.41), P = 0.513*	***0.41 (0.26- 0.66), P < 0.001***	*1.16 (0.78- 1.72), P = 0.471*
Codominant	*bb vs. BB*	*0.89 (0.45- 1.78), P = 0.748*	*1.59 (0.65- 3.89), P = 0.307*	*2.24 (0.96- 5.22), P = 0.063*	*0.71 (0.34- 1.50), P = 0.372*
	Bb vs. BB	*0.92 (0.62- 1.37), P =*	*1.33 (0.75- 2.33), P = 0.328*	*1.62 (0.96- 2.74), P = 0.071*	*0.82 (0.54- 1.24), P =*

		0.684			0.341
Allelic	B vs. b	1.06 (0.80- 1.40), P = 0.681	0.81 (0.55- 1.18), P = 0.266	**0.69 (0.48- 0.98), P = 0.037**	1.18 (0.87- 1.58), P = 0.284
	b vs. B	0.94 (0.71- 1.25), P = 0.681	1.24 (0.85- 1.82), P = 0.266	**1.45 (1.02- 2.08), P = 0.037**	0.85 (0.63- 1.15), P = 0.284

Tru9I (rs757343)

Genotypes and Alleles	Group I	Group II	Group III
UU (%)	119 (74.37)	199 (79.60)	63 (70.00)
Uu (%)	35 (21.88)	45 (18.00)	22 (24.44)
uu (%)	6 (3.75)	6 (2.40)	5 (5.56)
U (%)	273 (85.31)	443 (88.60)	148 (82.22)
u (%)	47 (14.69)	57 (11.40)	32 (17.78)
HWE Chi-squared value* (P- value)	2.59 (0.108)	2.97 (0.085)	2.42 (0.120)

Odds ratio (95% CI) and P- values

Genetic models		Groups II & III vs. group I	Group III vs. group I	Group III vs. group II	Group II vs. group I
Dominant	UU + Uu vs. uu	1.17 (0.42- 3.21), P = 0.767	0.66 (0.20- 2.24), P = 0.507	0.42 (0.12- 1.41), P = 0.159	1.58 (0.50- 5.00), P = 0.433
	uu vs. UU + Uu	0.86 (0.31- 2.38), P = 0.676	1.52 (0.45- 5.00), P = 0.507	2.38 (0.71- 8.33), P = 0.159	0.63 (0.20- 2.00), P = 0.433
Recessive	uu + Uu vs. UU	0.86 (0.56- 1.37), P = 0.511	1.24 (0.70- 2.21), P = 0.456	1.67 (0.97- 2.[illegible]9), P = 0.065	0.74 (0.47- 1.19), P = 0.217
	UU vs. uu + Uu	1.16 (0.73- 1.79), P = 0.511	0.81 (0.45- 1.43), P = 0.456	0.60 (0.35- 1.[illegible]3), P = 0.065	1.35 (0.84- 1.13), P = 0.217
Overdominant	Uu vs. UU + uu	0.88 (0.53- 1.39), P = 0.575	1.16 (0.63- 2.13), P = 0.642	1.47 (0.[illegible]3- 2.63), P = 0.189	0.78 (0.48- 1.29), P = 0.335
	UU + uu vs. Uu	1.14 (0.72- 1.89), P = 0.575	0.86 (0.47- 1.59), P = 0.642	0.68 (0.38- 1.21), P = 0.189	1.28 (0.78- 2.08), P = 0.335
Codominant	uu vs. UU	0.83 (0.30- 2.31), P = 0.725	1.57 (0.46- 5.36), P = 0.468	2.63 (0.78- 8.92), P = 0.120	0.60 (0.19- 1.90), P = 0.383
	Uu vs. UU	0.87 (0.55- 1.38), P = 0.554	1.19 (0.64- 2.20), P = 0.584	1.54 (0.86- 2.77), P = 0.144	0.77 (0.47- 1.26), P = 0.300
Allelic	U vs. u	1.14 (0.78- 1.67), P = 0.492	0.80 (0.49- 1.30), P = 0.364	**0.60 (0.37- 0.95), P = 0.031**	1.34 (0.88- 2.03), P = 0.169
	u vs. U	0.88 (0.60- 1.28), P = 0.492	1.25 (0.77- 2.04), P = 0.364	**1.67 (1.05- 2.70), P = 0.031**	0.75 (0.49- 1.14), P = 0.169

TaqI (rs731236)

Genotypes and Alleles	Group I	Group II	Group III
TT (%)	87 (54.38)	121 (48.40)	51 (56.67)
Tt (%)	56 (35.00)	96 (38.40)	29 (32.22)
tt (%)	17 (10.62)	33 (13.20)	10 (11.11)
T (%)	230 (71.88)	338 (67.60)	131 (72.78)
t (%)	90 (28.13)	162 (32.40)	49 (27.22)
HWE Chi-squared value* (P- value)	2.89 (0.089)	3.81 (0.051)	3.14 (0.076)

Odds ratio (95% CI) and P- values

Genetic models		Groups II & III vs. group I	Group III vs. group I	Group III vs. group II	Group II vs. group I
Dominant	TT + Tt vs. tt	0.82 (0.4[illegible]- 1.4[illegible]), P = 0.517	0.95 (0.42- 2.18), P = 0.905	1.22 (0.57- 2.58), P = 0.610	0.78 (0.42- 1.46), P = 0.438
	tt vs. TT + Tt	1.22 (0.67- 2.2[illegible]), P = 0.517	1.05 (0.46- 2.38), P = 0.905	0.82 (0.39- 1.75), P = 0.610	1.28 (0.69- 2.38), P = 0.438
Recessive	tt + Tt vs. TT	1.16 (0.80- 1.70), P = 0.429	0.91 (0.54- 1.53), P = 0.727	0.72 (0.44-1.17), P = 0.179	1.27 (0.85- 1.89), P = 0.238
	TT vs. tt + Tt	0.86 (0.59- 1.25), P = 0.429	1.10 (0.65- 1.85), P = 0.727	1.39 (0.86- 2.27), P = 0.179	0.79 (0.53- 1.18), P = 0.238
Overdominant	Tt vs. TT + tt	1.08 (0.73- 1.60), P = 0.702	0.88 (0.51- 1.53), P = 0.656	0.76 (0.46- 1.27), P = 0.298	1.16 (0.77- 1.75), P = 0.487
	TT + tt vs. Tt	0.93 (0.63- 1.37), P = 0.702	1.14 (0.65- 1.96), P = 0.656	1.32 (0.79- 21.17), P = 0.298	0.86 (0.57- 1.30), P = 0.487
Codominant	tt vs. TT	1.28 (0.69- 2.37), P = 0.435	1.00 (0.43- 2.36), P = 0.994	0.72 (0.33- 1.57), P = 0.407	1.40 (0.73- 2.67), P = 0.312
	Tt vs. TT	1.13 (0.75- 1.70), P = 0.559	0.883 (0.50- 1.56), P = 0.668	0.72 (0.42- 1.22), P = 0.217	1.23 (0.80- 1.89), P = 0.340
Allelic	T vs. t	0.87 (0.65- 1.17), P = 0.351	1.05 (0.70- 1.57), P = 0.829	1.28 (0.89- 1.87), P = 0.199	0.82 (0.60- 1.11), P = 0.196
	t vs. T	1.15 (0.59- 1.54), P = 0.351	0.95 (0.64- 1.43), P = 0.829	0.78 (0.54- 1.12), P = 0.199	1.22 (0.90- 1.67), P = 0.196

BglI (rs739837)

Genotypes and Alleles	Group I	Group II	Group III
GG (%)	98 (61.25)	160 (64.00)	60 (66.67)
Gg (%)	56 (35.00)	74 (29.60)	24 (26.66)
gg (%)	6 (3.75)	16 (6.40)	6 (6.67)
G (%)	252 (78.75)	394 (78.80)	144 (80.00)
g (%)	68 (21.25)	106 (21.20)	36 (20.00)
HWE Chi-squared value* (P- value)	0.34 (0.563)	3.25 (0.071)	2.50 (0.114)

Odds ratio (95% CI) and P- values

Genetic models		Groups II & III vs. group	Group III vs. group I	Group III vs. group II	Group II vs. group I

		I			
Dominant	*GG + Gg vs. gg*	*0.56 (0.22- 1.42), P = 0.223*	*0.55 (0.17- 1.74), P = 0.307*	*0.96 (0.36- 2.53), P = 0.930*	*0.57 (0.22- 1.49), P = 0.251*
	gg vs. GG + Gg	*1.79 (0.70- 4.55), P = 0.223*	*1.82 (0.58- 5.88), P = 0.307*	*1.04 (0.40- 2.78), P = 0.930*	*1.75 (0.67- 4.55), P = 0.251*
Recessive	*gg + Gg vs. GG*	*0.86 (0.59- 1.27), P = 0.454*	*0.79 (0.46- 1.36), P = 0.394*	*0.89 (0.54- 1.48), P = 0.650*	*0.89 (0.59- 1.34), P = 0.574*
	GG vs. gg + Gg	*1.16 (0.79- 1.70), P =0.454*	*1.27 (0.74- 2.17), P = 0.394*	*1.12 (0.68- 1.85), P = 0.650*	*1.12 (0.75- 1.70), P = 0.574*
Overdominant	*Gg vs. GG + gg*	*0.75 (0.51- 1.12), P = 0.164*	*0.68 (0.38- 1.19), P = 0.176*	*0.87 (0.50- 1.49), P = 0.599*	*0.78 (0.51- 1.19), P = 0.252*
	GG + gg vs. Gg	*1.33 (0.89- 1.96), P = 0.164*	*1.47 (0.84- 2.63), P = 0.176*	*1.15 (0.67- 2.00), P = 0.599*	*1.28 (0.84- 1.96), P = 0.252*
Codominant	*gg vs. GG*	*1.63 (0.64- 4.16), P = 0.303*	*1.63 (0.50- 5.30), P = 0.414*	*1.00 (0.37- 2.68), P = 1.000*	*1.63 (0.62- 4.32), P = 0.322*
	Gg vs. GG	*0.78 (0.52- 1.17), P = 0.229*	*0.70 (0.39- 1.25), P = 0.225*	*0.87 (0.50- 1.50), P = 0.603*	*0.81 (0.53- 1.24), P = 0.334*
Allelic	*G vs. g*	*1.02 (0.74- 1.42), P = 0.894*	*1.08 (0.69- 1.70), P = 0.741*	*1.08 (0.71- 1.64), P = 0.734*	*1.00 (0.71- 1.41), P = 0.986*
	g vs. AG	*0.98 (0.70- 1.35), P = 0.894*	*0.93 (0.59- 1.45), P = 0.741*	*0.93 (0.61- 1.41), P = 0.734*	*1.00 (0.71- 1.41), P = 0.986*

Table 5. Association of 5′ end's VDR polymorphisms- related genotypes with different clinical data in COVID-19 patients

Asymptomatic patients (group I)													
Variables	Status	FokI				CDX2				EcoRV			
		FF	Ff	ff	P	CC	Cc	cc	P	EE	Ee	ee	P
Gender	Male	48 (53.3)	30 (33.3)	12 (13.3)	0.070	41 (45.6)	38 (42.2)	11 (12.2)	0.339	61 (67.8)	24 (26.7)	5 (5.6)	0.911
	Female	27 (38.6)	36 (51.4)	7 (1.0)		32 (45.7)	24 (34.3)	14 (20.0)		46 (65.7)	19 (27.1)	5 (7.1)	
Hypertension	Yes	9 (47.4)	9 (47.4)	1 (5.3)	0.609	9 (47.4)	8 (42.1)	2 (10.5)	0.804	12 (63.2)	4 (21.4)	3 (15.8)	0.178
	No	66 (46.8)	57 (4.4)	18 (12.8)		64 (45.4)	54 (38.3)	23 (16.3)		95 (67.4)	39 (27.7)	7 (5.0)	
Diabetes	Yes	6 (37.5)	6 (37.5)	4 (25.0)	0.226	5 (31.2)	8 (50.0)	3 (18.8)	0.473	13 (81.2)	2 (12.5)	1 (6.2)	0.384
	No	69 (47.9)	60 (41.7)	15 (10.4)		68 (47.2)	54 (37.5)	22 (15.3)		94 (65.3)	41 (28.5)	9 (6.2)	
Asthma	Yes	8 (36.4)	10 (45.5)	4 (18.2)	0.457	9 (40.9)	10 (45.5)	3 (13.6)	0.785	13 (59.1)	9 (40.9)	0 (0.0)	0.158
	No	67 (48.6)	56 (40.6)	15 (10.9)		64 (46.4)	52 (37.7)	22 (15.9)		94 (68.1)	34 (24.6)	10 (7.2)	
Cardiovascular disease	Yes	6 (33.3)	10 (55.6)	2 (11.1)	0.405	8 (44.4)	7 (38.9)	3 (16.7)	0.990	9 (50.0)	7 (38.9)	2 (11.1)	0.257
	No	69 (48.6)	56 (39.4)	17 (12.0)		65 (45.8)	55 (38.7)	22 (15.5)		98 (69.0)	36 (25.4)	8 (5.6)	
Chronic renal disease	Yes	3 (27.3)	7 (63.6)	1 (9.1)	0.289	5 (45.5)	5 (45.5)	1 (9.1)	0.795	10 (90.9)	1 (9.1)	0 (0.0)	0.207
	No	72 (48.3)	59 (39.6)	18 (12.1)		68 (54.6)	57 (38.3)	24 (16.1)		97 (65.1)	42 (28.2)	10 (6.7)	
Malignancy	Yes	3 (33.3)	5 (55.6)	1 (11.1)	0.653	2 (22.2)	4 (44.4)	3 (33.3)	0.208	7 (77.8)	2 (22.2)	0 (0.0)	0.656
	No	72 (47.7)	61 (40.4)	18 (11.9)		71 (47.0)	58 (38.4)	22 (14.6)		100 (66.2)	41 (27.2)	10 (6.6)	
mild/ moderate patients (group II)													
Variables	Status	FokI				CDX2				EcoRV			
		FF	Ff	ff	P	CC	Cc	cc	P	EE	Ee	ee	P
Gender	Male	52 (36.6)	72 (50.7)	18 (12.7)	0.227	52 (36.6)	61 (43.0)	29 (20.4)	0.517	70 (49.3)	56 (39.4)	16 (11.3)	0.104
	Female	44 (40.7)	44 (40.7)	20 (18.5)		43 (39.8)	49 (45.4)	16 (14.8)		64 (59.3)	39 (36.1)	5 (4.6)	
Fever	Yes	50 (35.5)	65 (46.1)	26 (18.4)	0.227	58 (41.1)	58 (41.1)	25 (17.7)	0.484	77 (54.6)	54 (38.3)	10 (7.1)	0.695
	No	46 (42.2)	51 (46.8)	12 (11.0)		37 (33.9)	52 (47.7)	20 (18.3)		57 (52.3)	41 (37.6)	11 (10.1)	
Sore throat	Yes	31 (37.8)	37 (45.1)	14 (17.1)	0.845	28 (34.1)	40 (48.8)	14 (17.1)	0.557	43 (52.4)	34 (41.5)	5 (6.1)	0.553
	No	65 (38.7)	79 (47.0)	24 (14.3)		67 (39.9)	70 (41.7)	31 (18.5)		91 (54.2)	61 (36.3)	16 (9.5)	
Dry cough	Yes	56 (38.9)	69 (47.9)	19 (13.2)	0.580	61 (42.4)	59 (41.0)	24 (16.7)	0.254	79 (54.9)	52 (36.1)	13 (9.0)	0.749
	No	40 (37.7)	47 (44.3)	19 (17.9)		34 (32.1)	51 (48.1)	21 (19.8)		55 (51.9)	43 (40.6)	8 (7.5)	
Headache	Yes	19	24 (49.0)	6	0.803	17	21	11 (22.4)	0.649	51 (42.9)	23	5 (10.2)	0.243

		(38.8)		(12.2)		(34.7)	(42.9)				(46.9)		
	No	77 (38.3)	92 (45.8)	32 (15.9)		78 (38.8)	89 (44.3)	34 (16.9)		113 (56.2)	72 (35.8)	16 (8.0)	
Shortness of breath	Yes	15 (46.9)	10 (31.2)	7 (21.9)	0.167	10 (31.2)	14 (43.8)	8 (25.0)	0.487	15 (46.9)	13 (40.6)	4 (12.5)	0.574
	No	81 (37.2)	106 (48.6)	31 (14.2)		85 (39.0)	96 (44.0)	37 (17.0)		119 (54.6)	82 (37.6)	17 (7.8)	
Diarrhea	Yes	6 (31.6)	10 (52.6)	3 (15.8)	0.808	5 (26.3)	11 (57.9)	3 (15.8)	0.428	14 (73.7)	4 (21.1)	1 (5.3)	0.188
	No	90 (39.0)	106 (45.9)	35 (15.2)		90 (39.0)	99 (42.9)	42 (18.2)		120 (51.9)	91 (31.4)	20 (8.7)	
Myalgia	Yes	21 (33.9)	32 (51.6)	9 (14.5)	0.622	27 (43.5)	24 (38.7)	11 (17.7)	0.550	39 (62.9)	20 (32.3)	3 (4.8)	0.193
	No	75 (39.9)	84 (44.7)	29 (15.4)		68 (36.2)	86 (45.7)	34 (18.1)		95 (50.5)	75 (39.9)	18 (9.6)	
Fatigue	Yes	8 (30.8)	13 (50.0)	5 (19.2)	0.660	11 (42.3)	11 (42.3)	4 (15.4)	0.873	12 (46.2)	12 (46.2)	2 (7.7)	0.662
	No	88 (39.3)	103 (46.0)	33 (14.7)		84 (37.5)	99 (44.2)	41 (18.3)		122 (54.5)	83 (37.1)	19 (8.5)	
Nausea	Yes	10 (41.7)	10 (41.7)	4 (16.7)	0.887	7 (29.2)	14 (58.3)	3 (12.5)	0.328	15 (62.5)	6 (25.0)	3 (12.5)	0.349
	No	86 (38.1)	116 (46.9)	34 (15.0)		88 (38.9)	96 (42.5)	42 (18.6)		119 (52.7)	89 (39.4)	18 (8.0)	
Vomiting	Yes	7 (38.9)	9 (50.5)	2 (11.1)	0.847	9 (50.0)	5 (27.8)	4 (22.2)	0.352	9 (50.0)	7 (38.9)	2 (11.1)	0.896
	No	89 (38.4)	107 (46.1)	36 (15.5)		86 (37.1)	105 (45.3)	41 (17.7)		125 (53.9)	88 (37.9)	19 (8.2)	
Parageusia	Yes	5 (41.7)	6 (50.0)	1 (8.3)	0.794	5 (41.7)	4 (33.3)	3 (25.0)	0.700	8 (66.7)	3 (25.0)	1 (8.3)	0.618
	No	91 (38.2)	110 (46.2)	37 (15.5)		90 (37.8)	106 (44.5)	4 (17.6)0.700		126 (52.9)	92 (38.7)	20 (8.4)	
Hypertension	Yes	13 (29.5)	23 (52.3)	8 (18.2)	0.407	12 (27.3)	20 (45.5)	12 (27.3)	0.123	26 (59.1)	14 (31.8)	4 (9.1)	0.648
	No	83 (40.3)	93 (45.1)	30 (14.6)		83 (40.3)	90 (43.7)	33 (16.0)		108 (52.4)	81 (39.3)	17 (8.3)	
Diabetes	Yes	14 (31.8)	23 (52.3)	7 (15.9)	0.601	12 (27.3)	22 (50.0)	10 (22.7)	0.257	11 (25.0)	23 (52.3)	10 (22.7)	< **0.001**
	No	82 (39.8)	93 (45.1)	31 (15.0)		83 (40.3)	88 (42.7)	35 (17.0)		123 (59.7)	72 (35.0)	11 (5.3)	
Asthma	Yes	3 (21.4)	8 (57.1)	3 (21.4)	0.395	6 (42.9)	7 (50.0)	1 (7.1)	0.553	6 (42.9)	6 (42.9)	2 (14.3)	0.600
	No	93 (39.4)	108 (45.8)	35 (14.8)		89 (37.7)	103 (43.6)	44 (18.6)		128 (54.2)	89 (37.7)	19 (8.1)	
Cardiovascular disease	Yes	12 (50.0)	7 (29.2)	5 (20.8)	0.204	9 (37.5)	11 (45.8)	4 (16.7)	0.976	12 (50.0)	9 (37.5)	3 (12.5)	0.742
	No	84 (37.2)	109 (48.2)	33 (14.6)		86 (38.1)	99 (43.8)	41 (18.1)		122 (54.0)	86 (38.1)	18 (8.0)	
Chronic renal disease	Yes	18 (46.2)	15 (38.5)	6 (15.4)	0.509	14 (35.9)	19 (48.7)	6 (15.4)	0.793	20 (51.3)	17 (43.6)	2 (5.1)	0.602
	No	78 (37.0)	101 (47.9)	32 (15.2)		81 (38.4)	91 (43.1)	39 (18.5)		114 (54.0)	78 (37.0)	19 (9.0)	
Malignancy	Yes	4 (40.0)	5 (50.0)	1 (10.0)	0.895	5 (50.0)	5 (50.0)	0 (0.0)	0.308	7 (70.0)	1 (10.0)	2 (20.0)	0.114
	No	92 (38.3)	111 (46.2)	37 (15.4)		90 (37.5)	105 (43.8)	45 (18.8)		127 (52.9)	94 (39.2)	19 (7.9)	
severe and critical patients (group III)													
Variables	Status	FokI				CDX2				EcoRV			
		FF	Ff	ff	P	CC	Cc	cc	P	EE	Ee	ee	P
Gender	Male	19 (31.1)	27 (44.3)	15 (24.6)	0.286	16 (26.2)	25 (41.0)	20 (32.8)	0.206	26 (42.6)	31 (50.8)	4 (6.6)	0.832
	Female	11 (37.9)	15 (51.7)	3 (10.3)		12 (41.4)	12 (41.4)	5 (17.2)		13 (44.8)	15 (51.7)	1 (3.4)	
Fever	Yes	16 (30.8)	22 (42.3)	14 (26.9)	0.158	18 (34.6)	23 (44.2)	11 (21.2)	0.256	23 (44.2)	25 (48.1)	4 (7.7)	0.533
	No	14 (36.8)	20 (52.6)	4 (10.5)		10 (26.3)	14 (36.8)	14 (36.8)		16 (42.1)	21 (55.3)	1 (2.6)	
Sore throat	Yes	6 (23.1)	11 (42.3)	9 (34.6)	0.074	6 (23.1)	11 (42.3)	9 (34.6)	0.500	12 (46.2)	12 (46.2)	2 (7.7)	0.762
	No	24 (37.5)	31 (48.4)	9 (14.1)		22 (34.4)	26 (40.6)	16 (25.0)		27 (42.2)	34 (53.1)	3 (4.7)	
Dry cough	Yes	10 (22.7)	22 (50.0)	12 (27.3)	0.068	15 (34.1)	16 (36.4)	13 (29.5)	0.665	22 (50.0)	19 (43.2)	3 (6.8)	0.335
	No	20 (43.5)	20 (43.5)	6 (13.0)		13 (28.3)	21 (45.7)	12 (26.1)		17 (37.0)	27 (58.7)	2 (4.3)	
Headache	Yes	2 (20.0)	6 (60.0)	2 (20.0)	0.598	3 (30.0)	5 (50.0)	2 (20.0)	0.792	5 (50.0)	3 (30.0)	2 (20.0)	0.070
	No	28	36 (45.0)	16		25	32	23 (28.7)		34 (42.5)	43	3 (3.8)	

		(35.0)		(20.0)		(31.2)	(40.0)				(53.8)		
Shortness of breath	Yes	19 (32.2)	27 (45.8)	13 (22.0)	0.799	22 (37.3)	26 (44.1)	11 (18.6)	**0.022**	29 (49.2)	26 (44.1)	4 (6.8)	0.177
	No	11 (35.5)	15 (48.4)	5 (16.1)		6 (19.4)	11 (35.5)	14 (45.2)		10 (32.3)	20 (64.5)	1 (3.2)	
Diarrhea	Yes	3 (27.3)	5 (45.5)	3 (27.3)	0.789	4 (36.4)	3 (27.3)	4 (36.4)	0.598	4 (36.4)	6 (54.5)	1 (9.1)	0.798
	No	27 (34.2)	37 (46.8)	15 (19.0)		24 (30.4)	34 (43.0)	21 (26.6)		35 (44.3)	40 (50.6)	4 (5.1)	
Myalgia	Yes	5 (29.4)	8 (47.1)	4 (23.5)	0.892	4 (23.5)	9 (52.9)	4 (23.5)	0.539	6 (35.3)	9 (52.9)	2 (11.8)	0.410
	No	25 (34.2)	34 (46.6)	14 (19.2)		24 (32.9)	28 (38.4)	21 (27.8)		33 (45.2)	37 (50.7)	3 (4.1)	
Fatigue	Yes	12 (38.7)	13 (41.9)	6 (19.4)	0.724	12 (38.7)	12 (38.7)	7 (22.6)	0.496	16 (51.6)	14 (45.2)	1 (3.2)	0.464
	No	18 (30.5)	29 (49.2)	12 (20.3)		16 (27.1)	25 (42.4)	18 (30.5)		23 (39.)	32 (54.2)	4 (6.8)	
Nausea	Yes	4 (26.7)	8 (53.3)	3 (20.0)	0.814	5 (33.3)	3 (20.0)	7 (46.7)	0.117	4 (26.7)	10 (66.7)	1 (6.7)	0.360
	No	26 (34.7)	34 (45.3)	15 (20.0)		23 (30.7)	34 (45.3)	18 (24.0)		35 (46.7)	36 (48.0)	4 (5.3)	
Vomiting	Yes	2 (18.2)	7 (63.6)	2 (18.2)	0.437	0 (0.0)	6 (54.5)	5 (45.5)	0.053	4 (36.4)	6 (54.5)	1 (9.1)	0.798
	No	28 (35.4)	35 (44.3)	16 (20.3)		28 (35.4)	31 (39.2)	20 (25.3)		35 (44.3)	40 (50.6)	4 (5.1)	
Parageusia	Yes	12 (46.2)	11 (42.3)	3 (11.5)	0.196	8 (30.8)	11 (42.3)	7 (26.[illegible])	0.988	10 (38.5)	15 (57.7)	1 (3.8)	0.704
	No	18 (21.8)	31 (48.4)	15 (23.4)		20 (31.2)	26 (40.6)	18 ([illegible].1)		29 (45.3)	31 (48.4)	4 (6.2)	
Hypertension	Yes	14 (31.1)	17 (37.8)	14 (31.1)	**0.027**	15 (33.3)	13 (28.9)	17 ([illegible].8)	**0.036**	15 (33.3)	27 (60.0)	3 (6.7)	0.160
	No	16 (35.6)	25 (55.6)	4 (8.9)		13 (28.9)	24 ([illegible])	8 ([illegible].8)		24 (53.3)	19 (42.2)	2 (4.4)	
Diabetes	Yes	12 (37.5)	12 (37.5)	8 (25.0)	0.412	8 (25.0)	[illegible]	14 (43.8)	**0.042**	9 (28.1)	22 (68.8)	1 (3.1)	**0.045**
	No	18 (31.0)	30 (51.7)	10 (17.2)		20 (34.[illegible])	27 (46.6)	11 (19.0)		30 (51.7)	24 (41.4)	4 (6.9)	
Asthma	Yes	7 ()46.7	5 (33.3)	3 (20.0)	0.439	[illegible] ([illegible].7)	8 (53.3)	3 (20.0)	0.560	8 (53.3)	6 (40.0)	1 (6.7)	0.641
	No	23 (30.7)	37 (49.3)	15 (20.0)		[illegible] (32.0)	29 (38.7)	22 (29.3)		31 (41.3)	40 (53.3)	4 (5.3)	
Cardiovascular disease	Yes	4 (36.4)	3 (27.3)	4 (36.4)	0.256	6 (54.5)	4 (36.4)	1 (9.1)	0.145	6 (54.5)	5 (45.5)	0 (0.0)	0.566
	No	26 (32.9)	39 (49.4)	14 (17.[illegible])		22 (27.8)	33 (41.8)	24 (30.4)		33 (41.8)	41 (51.9)	5 (6.3)	
Chronic renal disease	Yes	8 (32.0)	10 (40.0)	[illegible] (28.[illegible])	0.483	10 (40.0)	10 (40.0)	5 (20.0)	0.440	10 (40.0)	15 (60.0)	0 (0.0)	0.280
	No	22 (33.8)	32 (49.2)	11 ([illegible])		18 (27.7)	27 (41.5)	20 (30.8)		29 (44.6)	31 (47.7)	5 (7.7)	
Malignancy	Yes	2 (20.0)	5 (5[illegible])	3 (30.0)	0.552	3 (30.0)	5 (50.0)	2 (20.0)	0.792	4 (40.0)	5 (50.0)	1 (10.0)	0.675
	No	28 (35.0)	[illegible] (46.[illegible])	15 (18.8)		25 (31.2)	32 (40.0)	23 (28.7)		34 (42.5)	42 (52.5)	4 (5.0)	

Table 6. Association of 3′ end’s VDR polymorphisms- related genotypes with different clinical data in COVID-19 patients

Asymptomatic patients (group I)																					
Variables	Status	ApaI				BsmI				Tru9I				TaqI				BglI			
		AA	Aa	aa	P	BB	Bb	bb	P	UU	Uu	uu	P	TT	Tt	tt	P	GG	Gg	gg	P
Gender	Male	29 (32.2)	47 (52.2)	14 (15.6)	0.543	34 (37.8)	44 (48.9)	12 (13.3)	0.150	70 (77.8)	17 (18.9)	3 (3.3)	0.534	46 (51.1)	36 (40.0)	8 (8.9)	0.293	52 (57.8)	33 (36.7)	5 (5.6)	0.308
	Female	22 (31.4)	41 (58.6)	7 (10.0)		29 (41.4)	38 (54.3)	3 (4.3)		49 (70.0)	18 (21.9)	3 (4.3)		41 (58.6)	20 (28.6)	9 (12.9)		46 (65.7)	23 (32.9)	1 (1.4)	
Hypertension	Yes	4 (21.1)	13 (68.4)	2 (10.5)	0.447	11 (57.9)	7 (36.8)	1 (5.3)	0.208	16 (84.2)	3 (15.8)	0 (0.0)	0.483	11 (57.9)	6 (31.6)	2 (10.5)	0.941	13 (68.4)	5 (26.3)	1 (5.3)	0.678
	No	47 (33.3)	75 (53.2)	19 (13.5)		52 (36.9)	75 (53.2)	14 (9.9)		103 (73.0)	32 (22.7)	6 (4.3)		76 (53.9)	50 (35.5)	15 (10.6)		85 (60.3)	51 (36.2)	5 (3.5)	
Diabetes	Yes	5 (31.2)	8 (50.0)	3 (18.8)	0.774	8 (50.0)	7 (43.8)	1 (6.2)	0.641	13 (81.2)	3 (18.8)	0 (0.0)	0.651	6 (37.5)	9 (56.2)	1 (6.2)	0.170	8 (50.0)	8 (50.0)	0 (0.0)	0.337
	No	46 (31.9)	80 (55.6)	18 (12.5)		55 (38.2)	75 (52.1)	14 (9.7)		106 (73.6)	32 (22.2)	6 (4.2)		81 (56.2)	47 (32.6)	16 (11.1)		90 (62.5)	48 (33.3)	6 (4.2)	
Asthma	Yes	8 (36.4)	10 (45.5)	4 (18.2)	0.583	11 (50.0)	9 (40.9)	2 (9.1)	0.531	16 (72.7)	5 (22.7)	1 (4.5)	0.970	13 (59.1)	8 (36.4)	1 (4.5)	0.605	13 (59.1)	8 (36.4)	1 (4.5)	0.963
	No	43 (31.2)	78 (56.5)	17 (12.3)		52 (37.7)	73 (52.9)	13 (9.4)		103 (74.6)	30 (21.7)	5 (3.6)		74 (3.6)	48 (34.8)	16 (11.6)		85 (61.6)	48 (34.8)	5 (3.6)	
Cardiovascular disease	Yes	5 (27.8)	10 (55.6)	3 (16.7)	0.860	9 (50.0)	7 (38.9)	2 (11.1)	0.535	15 (83.3)	3 (16.7)	0 (0.0)	0.540	11 (61.1)	5 (27.8)	2 (11.1)	0.788	13 (72.2)	4 (22.2)	1 (5.6)	0.467
	No	46 (32.4)	78 (54.9)	18 (12.7)		54 (38.0)	75 (52.8)	13 (9.2)		104 (73.2)	32 (22.5)	6 (4.2)		76 (53.5)	51 (35.9)	15 (10.6)		85 (59.9)	52 (36.6)	5 (3.5)	
Chronic renal disease	Yes	3 (27.3)	7 (63.6)	1 (9.1)	0.825	5 (45.5)	6 (54.5)	0 (0.0)	0.537	8 (72.7)	3 (27.3)	0 (0.0)	0.739	6 (54.5)	4 (36.4)	1 (9.1)	0.984	6 (54.5)	5 (45.5)	0 (0.0)	0.638
	No	48 (32.2)	81 (54.4)	20 (13.4)		58 (38.9)	76 (51.0)	15 (10.1)		111 (74.5)	32 (21.5)	6 (4.0)		81 (54.5)	52 (34.9)	16 (10.7)		92 (61.7)	51 (34.2)	6 (4.0)	
Malignancy	Yes	4 (44.4)	3 (33.3)	2 (2.22)	0.389	6 (66.7)	3 (33.3)	0 (0.0)	0.193	5 (55.6)	4 (44.4)	0 (0.0)	0.220	4 (44.4)	4 (44.4)	1 (11.1)	0.811	5 (55.6)	4 (44.4)	0 (0.0)	0.722
	No	47 (31.1)	85 (56.3)	19 (12.6)		57 (37.7)	79 (52.3)	15 (9.9)		114 (75.5)	31 (20.5)	6 (4.0)		83 (55.0)	52 (34.4)	16 (10.6)		93 (61.6)	52 (34.4)	6 (4.0)	

mild/ moderate patients (group II)

Variables	Status	ApaI AA	ApaI Aa	ApaI aa	P	BsmI BB	BsmI Bb	BsmI bb	P	Tru9I UU	Tru9I Uu	Tru9I uu	P	TaqI TT	TaqI Tt	TaqI tt	P	BglI GG	BglI Gg	BglI gg	P
Gender	Male	60 (42.3)	59 (41.5)	23 (16.2)	0.980	63 (44.4)	68 (47.9)	11 (7.7)	0.986	112 (78.9)	26 (18.3)	4 (2.8)	0.870	71 (50.0)	49 (34.5)	22 (15.5)	0.249	96 (67.6)	39 (27.5)	7 (4.9)	0.319
	Female	47 (43.5)	44 (40.7)	17 (15.7)		49 (45.4)	51 (47.2)	8 (7.4)		87 (80.6)	19 (17.6)	2 (1.9)		50 (46.3)	47 (43.5)	11 (10.2)		64 (59.3)	35 (32.4)	9 (8.3)	
Fever	Yes	59 (41.8)	60 (42.6)	22 (15.6)	0.885	60 (42.6)	70 (49.6)	11 (7.8)	0.717	108 (76.6)	29 (20.6)	4 (2.8)	0.405	61 (43.3)	62 (44.0)	18 (12.8)	0.109	82 (58.2)	50 (35.5)	9 (6.4)	0.065
	No	48 (44.0)	43 (39.4)	18 (16.5)		52 (47.7)	49 (45.0)	8 (7.3)		91 (83.5)	16 (14.7)	2 (1.8)		60 (55.0)	34 (31.2)	15 (13.8)		78 (71.6)	24 (22.0)	7 (6.4)	
Sore throat	Yes	39 (47.6)	31 (37.8)	12 (14.6)	0.568	34 (41.5)	42 (51.2)	6 (7.3)	0.722	71 (86.6)	9 (11.0)	2 (2.4)	0.129	37 (41.5)	32 (39.0)	13 (15.9)	0.627	52 (63.4)	24 (29.3)	6 (7.3)	0.918
	No	68 (40.5)	72 (42.9)	28 (16.7)		78 (46.4)	77 (45.8)	13 (7.7)		128 (76.2)	36 (21.4)	4 (2.4)		84 (50.0)	64 (38.1)	20 (11.9)		108 (64.3)	50 (29.8)	10 (6.0)	
Dry cough	Yes	62 (43.1)	59 (41.0)	23 (16.0)	0.995	64 (44.4)	70 (48.6)	10 (6.9)	0.872	111 (77.1)	30 (208)	3 (2.1)	0.382	72 (50.0)	50 (34.7)	22 (15.3)	0.288	92 (63.9)	43 (29.9)	9 (6.2)	0.990
	No	45 (42.5)	44 (41.5)	17 (16.0)		48 (45.3)	49 (46.2)	9 (8.5)		88 (83.0)	15 (14.2)	3 (2.8)		49 (46.2)	46 (43.4)	11 (10.4)		68 (64.2)	31 (29.2)	7 (6.6)	
Headache	Yes	23 (46.9)	17 (34.7)	9 (18.4)	0.582	21 (42.9)	24 (49.0)	4 (8.2)	0.951	40 (81.6)	7 (14.3)	2 (4.1)	0.544	26 (53.1)	18 (36.7)	5 (10.2)	0.694	34 (69.4)	13 (26.5)	2 (4.1)	0.612
	No	84 (41.8)	86 (42.8)	31 (15.4)		91 (45.3)	95 (47.3)	15 (7.5)		159 (79.1)	38 (18.9)	4 (2.0)		95 (47.3)	78 (38.8)	28 (13.9)		126 (62.7)	61 (30.3)	14 (7.0)	
Shortness of breath	Yes	14 (43.8)	13 (40.6)	5 (15.6)	0.993	17 (53.1)	12 (37.5)	3 (9.4)	0.471	27 (84.4)	5 (15.6)	0 (0.0)	0.577	15 (46.9)	12 (37.5)	6 (15.6)	0.910	23 (71.9)	7 (21.9)	2 (6.2)	0.578
	No	93 (42.7)	90 (41.3)	35 (16.1)		95 (43.6)	107 (49.1)	16 (7.3)		172 (78.9)	40 (18.3)	6 (2.8)		106 (48.6)	84 (38.5)	28 (12.8)		137 (62.8)	67 (30.7)	14 (6.4)	
Diarrhea	Yes	9 (47.4)	7 (36.8)	3 (15.8)	0.907	10 (52.6)	8 (42.1)	1 (5.3)	0.756	15 (78.9)	4 (21.1)	0 (0.0)	0.740	9 (47.4)	6 (31.6)	4 (21.1)	0.545	15 (78.9)	4 (21.1)	0 (0.0)	0.281
	No	98 (42.4)	96 (41.6)	37 (16.0)		102 (44.2)	111 (48.1)	18 (7.8)		184 (79.7)	41 (17.7)	6 (2.6)		112 (48.5)	90 (39.0)	29 (12.6)		145 (62.8)	70 (30.3)	16 (6.9)	
Myalgia	Yes	26 (41.9)	30 (48.4)	6 (9.7)	0.211	26 (41.9)	31 (50.0)	5 (8.1)	0.872	48 (77.4)	14 (22.6)	0 (0.0)	0.224	[illegible]	27 (43.5)	6 (9.7)	0.499	45 72.6()	12 (19.4)	5 (8.1)	0.121
	No	81 (43.1)	73 (38.8)	34 (18.1)		86 (45.7)	88 (46.8)	14 (7.4)		151 (80.3)	31 (16.5)	6 (3.2)		92 (48.[illegible])	69 (36.7)	27 (14.4)		115 (61.2)	62 (33.0)	11 (5.9)	
Fatigue	Yes	11 (42.3)	12 (46.2)	3 (11.5)	0.765	11 (42.3)	14 (53.8)	1 (3.8)	0.665	19 (73.1)	6 (23.1)	1 (3.8)	0.662	[illegible]	[illegible]	4 (15.4)	0.562	17 (65.4)	7 (26.9)	2 (7.7)	0.926
	No	96 (42.9)	91 (40.6)	37 (16.5)		101 (45.1)	105 (46.9)	18 (8.0)		180 (80.4)	39 (17.4)	5 (2.2)		111 (49.6)	84 (37.5)	29 (12.9)		143 (63.8)	67 (29.9)	14 (6.2)	
Nausea	Yes	8 (33.3)	11 (45.8)	5 (20.8)	0.582	9 (37.5)	14 (58.3)	1 (4.2)	0.504	17 (70.8)	6 (25.0)	1 (4.2)	0.516	9 ([illegible])	14 (58.3)	1 (4.2)	0.080	16 (66.7)	6 (25.0)	2 (8.3)	0.829
	No	99 (43.8)	92 (40.7)	35 (15.5)		103 (45.6)	105 (46.5)	18 (8.0)		182 (80.5)	39 (17.3)	5 (2.4)		112 ([illegible]9.6)	82 (36.3)	32 (14.2)		144 (63.7)	68 (30.1)	14 (6.2)	
Vomiting	Yes	8 (44.4)	6 (33.3)	4 (22.2)	0.679	6 (33.3)	11 (61.1)	1 (5.6)	0.492	16 (88.9)	2 (11.1)	0 (0.0)	[illegible]52	9 (50.0)	9 (50.0)	0 (0.0)	0.197	13 (72.2)	4 (22.2)	1 (5.6)	0.747
	No	99 (42.7)	7 (41.8)	36 (15.5)		106 (45.7)	108 (46.6)	18 (7.8)		183 (78.9)	43 (18.5)	6 (2.6)		112 (48.3)	87 (37.5)	33 (14.2)		147 (63.4)	70 (30.2)	15 (6.5)	
Parageusia	Yes	7 (58.3)	3 (25.0)	2 (16.7)	0.468	5 (41.7)	6 (50.0)	1 (8.3)	0.974	9 (75.0)	3 (25.0)	[illegible] (0.0)	[illegible]12	8 (66.7)	4 (33.3)	0 (0.0)	0.270	7 (58.3)	5 (41.7)	0 (0.0)	0.475
	No	100 (42.0)	100 (42.0)	38 (16.0)		107 (45.0)	113 (47.5)	18 (7.6)		190 (79.8)	42 (17.6)	6 (2.5)		113 (47.5)	92 (38.7)	33 (13.9)		153 (64.3)	69 (29.0)	16 (6.7)	
Hypertension	Yes	16 (36.4)	19 (43.2)	9 (20.5)	0.541	17 (38.6)	24 (54.5)	3 (6.8)	0.595	31 (70.5)	12 (27.3)	[illegible] (2.[illegible])	0.211	19 (43.2)	20 (45.5)	5 (11.4)	0.569	28 (63.6)	13 (29.5)	3 (6.8)	0.992
	No	91 (44.2)	84 (40.8)	31 (15.0)		95 (46.1)	95 (46.1)	16 (7.8)		168 (81.6)	33 ([illegible].0)	5 (2.4)		102 (49.5)	76 (36.9)	28 (13.6)		132 (64.1)	61 (29.6)	16 (6.3)	
Diabetes	Yes	18 (40.9)	21 (47.7)	5 (11.4)	0.518	22 (50.0)	18 (40.9)	4 (9.1)	0.612	35 (79.5[illegible]	[illegible]8 (18.2)	1 (2.3)	0.998	17 (38.6)	20 (45.5)	7 (15.9)	0.360	29 (65.9)	12 (27.3)	3 (6.8)	0.931
	No	89 (43.2)	82 (39.8)	35 (17.0)		90 (43.7)	101 (49.0)	15 (7.3)		[illegible]64 [illegible]79.6)	37 ([illegible])	5 (2.4)		104 (50.5)	76 (36.9)	26 (12.6)		131 (63.6)	62 (30.1)	13 (6.3)	
Asthma	Yes	6 (42.9)	5 (35.7)	3 (21.4)	0.826	7 (50.0)	7 (50.0)	0 (0.0)	0.539	[illegible]	3 (21.4)	1 (7.1)	0.447	5 (35.7)	6 (42.9)	3 (21.4)	0.514	9 (64.3)	3 (21.4)	2 (14.3)	0.412
	No	101 (42.8)	98 (41.5)	37 (15.7)		105 (44.5)	112 (47.5)	19 (8.1)		189 (80.1)	42 (17.8)	5 (2.1)		116 (49.2)	90 (38.1)	30 (12.7)		151 (64.0)	71 (30.1)	14 (5.9)	
Cardiovascular disease	Yes	9 (37.5)	13 (54.2)	2 (8.3)	0.327	13 (54.2)	9 (37.5)	2 (8.3)	0.575	19 (79.2)	3 (12.5)	2 (8.3)	0.114	9 (37.5)	11 (45.8)	4 (16.7)	0.528	14 (58.3)	9 (37.5)	1 (4.2)	0.638
	No	98 (43.4)	90 (39.8)	38 (16.8)		99 (43.8)	110 (48.7)	17 (7.5)		180 (79.6)	42 (18.6)	4 (1.8)		112 (49.6)	85 (37.6)	29 (12.8)		146 (64.6)	65 (28.8)	15 (6.6)	
Chronic renal disease	Yes	17 (43.6)	15 (38.5)	7 (17.9)	0.905	24 (61.5)	10 (25.6)	[illegible]5 (12[illegible]	**0.010**	33 (84.6)	6 (15.4)	0 (0.0)	0.489	18 (46.2)	19 (48.7)	2 (5.1)	0.164	27 (69.2)	9 (23.1)	3 (7.7)	0.612
	No	90 (42.7)	88 (41.7)	33 (15.6)		88 (41.7)	109 (51.7)	14 ([illegible]6)		166 (78.7)	39 (18.5)	6 (2.8)		103 (48.8)	77 (36.5)	31 (14.7)		133 (63.0)	65 (30.8)	13 (6.2)	
Malignancy	Yes	3 (30.0)	4 (40.0)	3 (30.0)	0.432	6 (60.0)	3 (30.0)	[illegible] ([illegible]0.0)	0.524	8 (80.0)	2 (20.0)	0 (0.0)	0.872	3 (30.0)	5 (50.0)	2 (20.0)	0.482	7 (70.0)	1 (10.0)	2 (20.0)	0.110
	No	104 (43.3)	99 (41.2)	37 (15.4)		106 (44.2)	116 ([illegible])	18 ([illegible])		191 (79.6)	43 (17.9)	6 (2.5)		118 (49.2)	91 (37.9)	31 (12.9)		153 (63.7)	73 (30.4)	14 (5.8)	

severe and critical patients (group III)

Variables	Status	ApaI AA	ApaI Aa	ApaI aa	P	BsmI B[illegible]	BsmI [illegible]	BsmI bb	P	Tru9I UU	Tru9I Uu	Tru9I uu	P	TaqI TT	TaqI Tt	TaqI tt	P	BglI GG	BglI Gg	BglI gg	P
Gender	Male	17 (27.9)	37 (60.7)	7 (11.5)	0.159	[illegible] (34.4)	31 (50.8)	9 (14.8)	0.360	42 (68.9)	16 (26.2)	3 (4.9)	0.810	34 (55.7)	20 (32.8)	7 (11.5)	0.966	41 (67.2)	16 (26.2)	4 (6.6)	0.987
	Female	14 (48.3)	13 (44.8)	2 (6.9)		8 ([illegible])	19 (65.5)	2 (6.9)		21 (72.4)	6 (20.7)	2 (6.9)		17 (58.6)	9 (31.0)	3 (10.3)		19 (65.5)	8 (27.6)	2 (6.9)	
Fever	Yes	14 (26.9)	32 (61.5)	6 (11.5)	0.2[illegible]	19 (36.5)	28 (53.8)	5 (9.6)	0.482	35 (67.3)	15 (28.8)	2 (3.8)	0.417	25 (48.1)	21 (40.4)	6 (11.5)	0.124	36 (69.2)	14 (26.9)	2 (3.8)	0.451
	No	17 (44.7)	18 (47.4)	3 (7.9)		10 ([illegible])	22 (57.9)	6 (15.8)		28 (73.7)	7 (18.4)	3 (7.9)		26 (68.4)	8 (21.1)	4 (10.5)		24 (63.2)	10 (26.3)	4 (10.5)	
Sore throat	Yes	11 (42.3)	11 (42.3)	4 (15.4)	0.238	6 (23.1)	17 (65.4)	3 (11.5)	0.450	17 (65.4)	8 (30.8)	1 (3.8)	0.637	13 (50.0)	9 (34.6)	4 (15.4)	0.621	18 (69.2)	7 (26.9)	1 (3.8)	0.789
	No	20 (31.2)	39 (60.9)	[illegible] (7.[illegible])		23 (35.9)	33 (51.6)	8 (12.5)		46 (71.9)	14 (21.9)	4 (6.2)		38 (59.4)	20 (31.2)	6 (9.4)		42 (65.6)	17 (26.6)	5 (7.8)	
Dry cough	Yes	13 (29.5)	26 (59.1)	5 (11.4)	0.621	16 (36.4)	24 (54.5)	4 (9.1)	0.559	26 (59.1)	14 (31.8)	4 (9.1)	0.070	23 (52.3)	15 (34.1)	6 (13.6)	0.644	27 (61.4)	14 (31.8)	3 (6.8)	0.543
	No	18 (39.1)	24 (52.2)	4 (8.7)		13 (28.3)	28 (56.5)	7 (15.2)		37 (80.4)	8 (17.4)	1 (2.2)		28 (60.9)	14 (30.4)	4 (8.7)		33 (71.7)	10 (21.7)	3 (6.5)	
Headache	Yes	1 (10.0)	8 (80.0)	1 (10.0)	0.208	4 (40.0)	6 (60.0)	0 (0.0)	0.443	6 (60.0)	3 (30.0)	1 (10.0)	0.704	5 (50.0)	3 (30.0)	2 (20.0)	0.636	6 (60.0)	3 (30.0)	1 (10.0)	0.857
	No	30 (37.5)	42 (52.5)	8 (10.0)		25 (31.2)	44 (55.0)	11 (13.8)		57 (71.2)	19 (23.8)	4 (5.0)		46 (57.5)	26 (32.5)	8 (10.0)		54 (67.5)	21 (26.2)	5 (6.2)	
Shortness of breath	Yes	11 (18.6)	41 (69.5)	7 (11.9)	**< 0.001**	23 (39.0)	30 (50.8)	6 (10.2)	0.157	39 (66.1)	16 (27.1)	4 (6.8)	0.513	30 (50.8)	22 (37.3)	7 (11.9)	0.290	41 (69.5)	15 (25.4)	3 (5.1)	0.623
	No	20 (64.5)	9 (29.0)	2 (6.5)		6 (19.4)	20 (64.5)	5 (16.1)		24 (77.4)	6 (19.4)	1 (3.2)		21 (67.7)	7 (22.6)	3 (9.7)		19 (61.3)	9 (29.0)	3 (9.7)	
Diarrhea	Yes	5 (45.5)	6 (54.5)	0 (0.0)	0.428	3 (27.3)	7 (63.6)	1 (9.1)	0.842	6 (54.5)	4 (36.4)	1 (9.1)	0.487	5 (45.5)	4 (36.4)	2 (18.2)	0.635	8 (72.7)	3 (27.3)	0 (0.0)	0.636
	No	26 (32.9)	44 (55.7)	9 (11.4)		26 (32.9)	43 (54.4)	10 (12.2)		57 (72.2)	18 (22.8)	4 (5.1)		46 (58.2)	25 (31.6)	8 (10.1)		52 (65.8)	21 (26.6)	6 (7.6)	
Myalgia	Yes	8 (47.1)	8 (47.1)	1 (5.8)	0.450	4 (23.5)	8 (47.1)	5 (29.4)	0.054	15 (88.2)	2 (11.8)	0 (0.0)	0.170	14 (82.4)	2 (11.8)	1 (5.9)	0.058	11 (64.7)	5 (29.4)	1 (5.9)	0.956
	No	23 (31.5)	42 (57.5)	8 (11.0)		25 (34.2)	42 (57.5)	6 (8.2)		48 (65.8)	20 (27.4)	5 (6.8)		37 (50.7)	27 (37.0)	9 (12.3)		49 (67.1)	19 (26.0)	5 (6.8)	
Fatigue	Yes	9 (29.0)	19 (61.3)	3 (9.7)	0.709	7 (22.6)	19 (61.3)	5 (16.1)	0.327	20 (64.5)	9 (29.0)	2 (6.5)	0.712	15 (48.4)	13 (41.9)	3 (9.7)	0.360	21 (67.7)	8 (25.8)	2 (6.5)	0.988
	No	22 (37.3)	31 (52.5)	6 (10.2)		22 (37.3)	31 (52.5)	6 (10.2)		43 (72.9)	13 (22.0)	3 (5.1)		36 (61.0)	16 (27.1)	7 (11.9)		39 (66.1)	16 (27.1)	4 (6.8)	
Nausea	Yes	9 (60.0)	6 (40.0)	0 (0.0)	0.050	5 (33.3)	7 (46.7)	3 (20.0)	0.562	13 (86.7)	1 (6.7)	1 (6.7)	0.214	8 (53.3)	5 (33.3)	2 (13.3)	0.941	10 (66.7)	5 (33.3)	0 (0.0)	0.472
	No	22 (29.3)	44 (58.7)	9 (12.0)		24 (32.0)	43 (57.3)	8 (10.7)		50 (66.7)	21 (28.0)	4 (5.3)		43 (57.3)	24 (32.0)	8 (10.7)		50 (66.7)	19 (25.3)	6 (8.0)	
Vomiting	Yes	4 (364)	6 (54.5)	1 (9.1)	0.987	4 (36.4)	7 (63.6)	0 (0.0)	0.418	4 (36.4)	6 (54.5)	1 (9.1)	**0.031**	4 (36.4)	5 (45.5)	2 (18.2)	0.340	7 (63.6)	4 (36.4)	0 (0.0)	0.523
	No	27 (34.2)	44 (55.7)	8 (10.1)		25 (31.6)	43 (54.4)	11 (13.9)		59 (74.7)	16 (20.3)	4 (5.1)		47 (59.5)	24 (30.4)	8 (10.1)		53 (67.1)	20 (25.3)	6 (7.6)	
Parageusia	Yes	7 (26.9)	16 (61.5)	3 (11.5)	0.630	6 (23.1)	17 (65.4)	3 (11.5)	0.450	19 (73.1)	7 (26.9)	0 (0.0)	0.337	13 (50.0)	11 (42.3)	2 (7.7)	0.401	19 (73.1)	5 (19.2)	2 (7.7)	0.594
	No	24 (37.5)	34 (53.1)	6 (9.4)		23 (35.9)	33 (51.6)	8 (12.5)		44 (68.8)	15 (23.4)	5 (7.8)		38 (59.4)	18 (28.1)	8 (12.5)		41 (64.1)	19 (29.7)	4 (6.2)	
Hypertension	Yes	18 (40.0)	24 (53.3)	3 (6.7)	0.389	15 (33.3)	24 (53.3)	6 (13.3)	0.902	30. (66.7)	13 (28.9)	2 (4.4)	0.586	25 (55.6)	15 (33.3)	5 (11.1)	0.973	29 (64.4)	14 (31.1)	2 (4.4)	0.497
	No	13 (28.9)	26 (57.8)	6 (13.3)		14 (31.1)	26 (57.8)	5 (11.1)		33 (73.3)	9 (20.0)	3 (6.7)		26 (57.8)	14 (31.1)	5 (11.1)		31 (68.9)	10 (22.2)	4 (8.9)	
Diabetes	Yes	12	19	1	0.271	10	18	4	0.989	23	6	3	0.370	19	11	2	0.551	21	9	2	0.970

		(37.5)	(59.4)	(3.1)		(31.2)	(56.2)	(12.5)		(71.9)	(18.8)	(9.4)		(59.4)	(34.4)	(6.2)		(65.6)	(28.1)	(6.2)	
	No	19 (32.8)	31 (53.4)	8 (13.8)		19 (32.8)	32 (55.2)	7 (12.1)		40 (69.0)	16 (27.6)	2 (3.4)		32 (55.2)	18 (31.0)	8 (13.8)		39 (67.2)	15 (25.9)	4 (6.9)	
Asthma	Yes	6 (40.0)	5 (33.3)	4 (26.7)	**0.034**	7 (46.7)	7 (46.7)	1 (6.7)	0.391	13 (86.7)	1 (6.7)	1 (6.7)	0.214	9 (60.0)	6 (40.0)	0 (0.0)	0.305	7 (46.7)	6 (40.0)	2 (13.3)	0.176
	No	25 (33.3)	45 (60.0)	5 (6.7)		22 (29.3)	43 (57.3)	10 (13.3)		50 (66.7)	21 (28.0)	4 (5.3)		42 (56.0)	23 (30.7)	10 (13.3)		53 (70.7)	18 (24.0)	4 (5.3)	
Cardiovascular disease	Yes	7 (63.6)	4 (36.4)	0 (0.0)	0.075	1 (9.1)	8 (72.7)	2 (18.2)	0.211	8 (72.7)	3 (27.3)	0 (0.0)	0.687	7 (63.6)	3 (27.3)	1 (9.1)	0.883	8 (72.7)	2 (18.2)	1 (9.1)	0.772
	No	24 (30.4)	46 (58.2)	9 (11.4)		28 (35.4)	42 (53.2)	9 (11.4)		55 (69.6)	19 (24.1)	5 (6.3)		44 (55.7)	26 (32.9)	9 (11.4)		52 (65.8)	22 (27.8)	5 (6.3)	
Chronic renal disease	Yes	7 (28.0)	15 (60.0)	3 (12.0)	0.712	8 (32.0)	10 (40.0)	7 (28.0)	**0.014**	21 (84.0)	4 (16.0)	0 (0.0)	0.142	14 (56.0)	9 (36.0)	2 (8.0)	0.795	20 (80.0)	4 (16.0)	1 (4.0)	0.250
	No	24 (36.9)	35 (53.8)	6 (9.2)		21 (32.3)	40 (61.5)	4 (6.2)		42 (64.6)	18 (27.7)	5 (7.7)		37 (56.9)	20 (30.8)	8 (12.3)		40 (61.5)	20 (30.8)	5 (7.7)	
Malignancy	Yes	4 (40.0)	5 (50.0)	1 (10.0)	0.922	2 (20.0)	5 (50.0)	3 (30.0)	0.174	10 (100.0)	0)0.0)	0 (0.0)	0.090	5 (50.0)	4 (40.0)	1 (10.0)	0.856	5 (50.0)	4 (40.0)	1 (10.0)	0.495
	No	27 (33.8)	45 (56.2)	8 (10.0)		27 (33.8)	45 (56.2)	8 (10.0)		53 (66.2)	22 (27.5)	5 (6.2)		46 (57.5)	25 (31.2)	9 (11.2)		55 (68.8)	20 (25.0)	5 (6.2)	

Table 7. Significant association of VDR gene polymorphisms with some clinical symptom and comorbidities in COVID-19 suffered patients

Mild/ moderate patients			
BsmI and chronic renal disease			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*BB + Bb vs. bb*	0.189	0.48 (0.16- 1.43)
	bb vs. BB + Bb		2.08 (0.70- 6.25)
Recessive	*bb + Bb vs. BB*	**0.024**	0.45 (0.22- 0.90)
	BB vs. bb + Bb		2.22 (1.11- 4.55)
Overdominant	*Bb vs. BB + bb*	**0.004**	0.32 (0.15- 0.70)
	BB + bb vs. Bb		3.13 (1.43- 6.67)
Codominant	*bb vs. BB*	0.[illegible]36	1.31 (0.43- 4.00)
	Bb vs. BB	**0.007**	0.34 (0.15- 0.74)
Allelic	*B vs. b*	0.234	1.39 (0.81- 2.41)
	b vs. B		0.72 (0.42- 1.24)
EcoRV and diabetes			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*EE + Ee vs. ee*	**< 0.001**	0.19 (0.08-0.49)
	ee vs. EE + Ee		5.26 (2.04- 12.50)
Recessive	*ee + Ee vs. EE*	**< 0.001**	4.45 (2.13- 9.29)
	EE vs. ee + Ee		0.23 (0.11- 0.47)
Overdominant	*Ee vs. EE + ee*	**0.034**	2.04 (1.06- 3.93)
	EE + ee vs. Ee		0.49 (0.26- 0.94)
Codominant	*ee vs. EE*	**< 0.001**	10.17 (3.54- 29.21)
	Ee vs. EE	**0.001**	3.57 (1.65- 7.75)
Allelic	*E vs. e*	**< 0.001**	0.31 (0.19- 0.50)
	e vs. E		3.23 (2.00- 5.26)
Severe and critical patients			
ApaI and shortness of breath			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*AA + Aa vs. aa*	0.423	0.51 (0.10- 2.63)
	aa vs. AA + Aa		1.96 (0.38- 10.00)
Recessive	*aa + Aa vs. AA*	**< 0.001**	7.93 (2.96- 21.25)
	AA vs. aa + Aa		0.13 (0.05- 0.34)
Overdominant	*Aa vs. AA + aa*	**< 0.001**	5.57 (2.15- 14.44)
	AA + aa vs. Aa		0.18 (0.07- 0.47)
Codominant	*aa vs. AA*	**0.037**	6.36 (1.12- 36.08)
	Aa vs. AA	**< 0.001**	8.28 (2.96- 23.21)
Allelic	*A vs. a*	**0.001**	0.30 (0.15- 0.62)
	a vs. A		3.33 (1.61- 6.67)
ApaI and asthma			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*AA + Aa vs. aa*	**0.029**	0.20 (0.05- 0.85)
	aa vs. AA + Aa		5.00 (1.18- 20.00)
Recessive	*aa + Aa vs. AA*	0.621	0.75 (0.24- 2.34)
	AA vs. aa + Aa		1.33 (0.43- 4.17)
Overdominant	*Aa vs. AA + aa*	0.065	0.33 (0.10- 1.07)
	AA + aa vs. Aa		3.03 (0.94- 10.00)
Codominant	*aa vs. AA*	0.137	3.33 (0.68- 16.32)
	Aa vs. AA	0.240	0.46 (0.13- 1.67)
Allelic	*A vs. a*	0.493	0.76 (0.34- 1.68)
	a vs. A		1.32 (0.60- 2.94)
BsmI and chronic renal disease			
Genetic models		P- value	Odds ratio (95 % CI)

Dominant	*BB + Bb vs. bb*	**0.009**	0.17 (0.04- 0.64)
	bb vs. BB + Bb		5.88 (1.56- 25.00)
Recessive	*bb + Bb vs. BB*	0.978	1.01 (0.38- 2.72)
	BB vs. bb + Bb		0.99 (0.37- 2.63)
Overdominant	*Bb vs. BB + bb*	0.069	0.42 (0.16- 1.07)
	BB + bb vs. Bb		2.38 (0.94- 6.25)
Codominant	*bb vs. BB*	**0.043**	4.59 (1.05- 20.06)
	Bb vs. BB	0.440	0.66 (0.23- 1.91)
Allelic	*B vs. b*	0.176	0.63 (0.33- 1.23)
	b vs. B		1.59 (0.81- 3.03)
FokI and hypertension			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*FF + Ff vs. ff*	**0.013**	0.22 (0.07- 0.72)
	ff vs. FF + Ff		4.55 (1.39- 14.29)
Recessive	*ff + Ff vs. FF*	0.655	1.22 (0.51- 2.94)
	FF vs. ff + Ff		0.82 (0.34- 1.96)
Overdominant	*Ff vs. FF + ff*	0.093	0.49 (0.21- 1.13)
	ff + FF vs. Ff		2.04 (0.89- 4.76)
Codominant	*ff vs. FF*	**0.040**	4.00 (1.07- 15.01)
	Ff vs. FF	0.601	0.78 (0.30- 2.00)
Allelic	*F vs. f*	0.072	0.58 (0.32- 1.05)
	f vs. F		1.72 (0.95- 3.13)
CDX2 and shortness of breath			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*CC + Cc vs. cc*	**0.009**	3.59 (1.37- 9.42)
	cc vs. CC + Cc		0.28 (0.11- 0.73)
Recessive	*cc + Cc vs. CC*	0.086	0.40 (0.14- 1.14)
	CC vs. cc + Cc		2.50 (0.88- 7.14)
Overdominant	*Cc vs. CC + cc*	0.433	1.43 (0.58- 3.52)
	CC + cc vs. Cc		0.70 (0.28- 1.72)
Codominant	*cc vs. CC*	**0.012**	0.21 (0.07- 0.71)
	Cc vs. CC	0.452	0.65 (0.21- 2.03)
Allelic	*C vs. c*	**0.005**	2.47 (1.31- 4.66)
	c vs. C		0.41 (0.22- 0.76)
CDX2 and hypertension			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*CC + Cc vs. cc*	**0.038**	0.36 (0.14- 0.94)
	cc vs. CC + Cc		2.78 (1.06- 7.14)
Recessive	*cc + Cc vs. CC*	0.649	0.81 (0.33- 1.99)
	CC vs. cc + Cc		1.24 (0.50- 3.03)
Overdominant	*Cc vs. CC + cc*	**0.020**	0.36 (0.15- 0.85)
	CC + cc vs. Cc		2.78 (1.18- 6.67)
Codominant	*cc vs. CC*	0.286	1.84 (0.60- 5.63)
	Cc vs. CC	0.140	0.47 (0.17- 1.28)
Allelic	*C vs. c*	0.297	0.73 (0.41- 1.32)
	c vs. C		1.37 (0.76- 2.44)
CDX2 and diabetes			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*CC + Cc vs. cc*	**0.014**	0.30 (0.12- 0.79)
	cc vs. CC + Cc		3.33 (1.27- 8.33)
Recessive	*cc + Cc vs. CC*	0.354	1.58 (0.60- 4.15)
	CC vs. cc + Cc		0.63 (0.24- 1.67)
Overdominant	*Cc vs. CC + cc*	0.161	0.52 (0.21- 1.29)
	CC + cc vs. Cc		1.92 (0.78- 4.76)
Codominant	*cc vs. CC*	**0.046**	3.18 (1.02- 9.93)
	Cc vs. CC	0.890	0.93 (0.31- 2.77)
Allelic	*C vs. c*	**0.029**	0.50 (0.27- 0.93)
	c vs. C		2.00 (1.08- 3.70)
EcoRV and diabetes			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*EE + Ee vs. ee*	0.466	2.30 (0.25- 21.47)
	ee vs. EE + Ee		0.44 (0.05- 4.00)
Recessive	*ee + Ee vs. EE*	**0.033**	2.74 (1.08- 6.92)
	EE vs. ee + Ee		0.41 (0.15- 0.93)
Overdominant	*Ee vs. EE + ee*	**0.015**	3.12 (1.25- 7.76)
	EE + ee vs. Ee		0.32 (0.13- 0.80)

Codominant	*ee vs. EE*	0.877	0.83 (0.08- 8.43)
	Ee vs. EE	**0.020**	3.06 (1.19- 7.85)
Allelic	*E vs. e*	0.171	0.64 (0.33- 1.22)
	e vs. E		1.56 (0.82- 3.03)

Table 8. Association of VDR gene polymorphisms- related genotypes with clinical data in COVID-19 patients with positive criteria of signs and symptoms

5′ end's VDR polymorphisms													
Variables	Status	FokI				CDX2				EcoRV			
		FF	Ff	ff	P	CC	Cc	cc	P	EE	Ee	ee	P
Gender	Male	76 (37.4)	96 (47.3)	31 (15.3)	0.766	67 (33.0)	89 (43.8)	47 (23.2)	0.217	99 (48.8)	86 (42.4)	18 (8.9)	0.468
	Female	50 (36.5)	62 (45.3)	25 (18.2)		56 (40.9)	58 (42.3)	23 (16.8)		74 (54.0)	55 (40.1)	8 (5.8)	
Fever	Yes	65 (33.7)	88 (45.6)	40 (20.7)	**0.042**	70 (36.3)	88 (45.6)	35 (18.1)	0.390	91 (47.2)	84 (43.5)	18 (9.3)	0.190
	No	61 (41.5)	70 (47.6)	16 (10.9)		53 (36.1)	59 (40.1)	35 (23.8)		82 (55.8)	57 (38.8)	8 (5.4)	
Sore throat	Yes	37 (34.3)	51 (47.2)	20 (18.5)	0.685	33 (30.6)	56 (51.9)	19 (17.6)	0.0[illegible]	56 (51.9)	44 (40.7)	8 (7.4)	0.970
	No	89 (38.4)	107 (46.1)	36 (15.5)		90 (38.8)	91 (39.2)	51 (22.[illegible])		117 (50.4)	97 (41.8)	18 (7.8)	
Dry cough	Yes	66 (35.1)	96 (48.4)	31 (16.5)	0.680	76 (404)	75 (39.9)	37 (19.7)	0.187	101 (53.7)	71 (37.8)	16 (8.5)	0.291
	No	60 (39.5)	67 (44.1)	25 (16.4)		47 (30.9)	72 (47.4)	33 (21.7)		72 (47.4)	70 (46.1)	10 (6.6)	
Headache	Yes	25 (42.4)	26 (44.1)	8 (13.6)	0.607	19 (3[illegible]2)	20 ([illegible])	20 (33.9)	**0.019**	26 (44.1)	27 (45.8)	6 (10.2)	0.458
	No	101 (35.9)	132 (47.0)	48 (17.1)		104 (37.0)	127 (45.2)	50 (17.8)		147 (52.3)	114 (40.6)	20 (7.1)	
Shortness of breath	Yes	35 (38.9)	37 (41.1)	18 (20.0)	0.408	30 (33.3)	38 (42.2)	22 (24.4)	0.552	43 (47.8)	37 (41.1)	10 (11.1)	0.340
	No	91 (36.4)	121 (48.4)	38 (15.2)		93 (37.2)	109 (43.6)	48 (19.2)		130 (52.0)	104 (41.6)	16 (6.4)	
Diarrhea	Yes	8 (26.7)	15 (50.0)	[illegible] (23.3)	0.370	8 (26.7)	15 (50.0)	7 (23.3)	0.524	17 (56.7)	11 (36.7)	2 (6.7)	0.802
	No	118 (38.1)	143 (46.1)	4[illegible] (15.8)		115 (37.1)	132 (42.6)	63 (20.3)		156 (50.3)	130 (41.9)	24 (7.7)	
Myalgia	Yes	26 (39.2)	40 ([illegible].6)	13 (16.5)	0.650	31 (39.2)	33 (41.8)	15 (19.0)	0.800	45 (57.0)	29 (36.7)	5 (6.3)	0.462
	No	100 (38.[illegible])	1[illegible]8 (4[illegible].2)	43 (16.5)		92 (35.2)	114 (43.7)	55 (21.1)		128 (49.0)	112 (42.9)	21 (8.0)	
Fatigue	Yes	24 (42.1)	19 (33.3)	14 (24.6)	0.057	24 (42.1)	24 (42.1)	9 (15.8)	0.484	32 (56.1)	22 (38.6)	3 (5.3)	0.601
	No	102 (36.0)	139 (49.1)	42 (14.8)		99 (35.0)	123 (43.5)	61 (21.6)		141 (49.8)	119 (42.0)	23 (8.1)	
Nausea	Yes	14 (35.9)	18 (46.2)	7 (17.9)	0.963	12 (30.8)	17 (43.6)	10 (25.6)	0.636	19 (48.7)	16 (41.0)	4 (10.3)	0.805
	No	112 (37.2)	140 46.5()	49 (16.3)		111 (36.9)	130 (43.2)	60 (19.9)		154 (51.2)	125 (41.5)	22 (7.3)	
Vomiting	Yes	6 (20.7)	18 (62.1)	5 (17.2)	0.138	10 (34.5)	12 (41.4)	7 (24.1)	0.885	11 (37.9)	16 (55.2)	2 (6.9)	0.286
	No	120 (38.6)	140 (45.0)	51 (16.4)		113 (36.3)	135 (43.4)	63 (20.3)		162 (52.1)	125 (40.2)	24 (7.7)	
Parageusia	Yes	17 (44.7)	17 (44.7)	4 (10.5)	0.444	13 (34.2)	15 (39.5)	10 (26.3)	0.648	18 (47.4)	18 (47.4)	2 (5.3)	0.677
	No	109 (36.1)	141 (46.7)	52 (17.2)		110 (36.4)	132 (43.7)	60 (19.9)		155 (51.3)	123 (40.7)	24 (7.9)	
Hypertension	Yes	28 (31.5)	39 (43.8)	22 (24.7)	**0.045**	28 (31.5)	32 (36.0)	29 (32.6)	**0.005**	40 (44.9)	42 (47.2)	7 (7.9)	0.408
	No	98	119	34		95	115	41		133 (53.0)	99	19 (7.6)	

		(39.0)	(47.4)	(13.5)		(37.8)	(45.8)	(16.3)			(39.4)		
Diabetes	Yes	26 (34.2)	35 (46.1)	15 (19.7)	0.653	20 (26.3)	32 (42.1)	24 (31.6)	**0.015**	20 (26.3)	45 (59.2)	11 (14.5)	**< 0.001**
	No	100 (37.9)	123 (46.6)	41 (15.5)		103 (39.0)	115 (43.6)	46 (17.4)		153 (58.0)	96 (36.4)	15 (5.7)	
Asthma	Yes	12 (41.4)	12 (41.4)	5 (17.2)	0.840	11 (37.9)	13 (44.8)	5 (17.2)	0.897	14 (48.3)	13 (44.8)	2 (6.9)	0.927
	No	114 (36.7)	146 (46.9)	51 (16.4)		112 (36.0)	134 (43.1)	65 (20.9)		159 (51.1)	128 (41.2)	24 (7.7)	
Cardiovascular disease	Yes	18 (51.4)	12 (34.3)	5 (14.3)	0.171	15 (42.9)	16 (45.7)	4 (11.4)	0.345	22 (62.9)	11 (31.4)	2 (5.7)	0.326
	No	108 (35.4)	146 (47.9)	51 (16.7)		108 (35.4)	131 (43.0)	66 (21.6)		151 (49.5)	130 (42.6)	24 (7.9)	
Chronic renal disease	Yes	24 (37.5)	26 (40.6)	16 (21.9)	0.371	25 (39.1)	27 (42.2)	12 (18.8)	0.847	32 (50.0)	29 (45.3)	3 (4.7)	0.550
	No	102 (37.0)	132 (47.8)	42 (15.2)		98 (35.5)	120 (43.5)	58 (21.0)		141 (51.1)	112 (40.6)	23 (8.3)	
Malignancy	Yes	6 (30.0)	11 (55.0)	3 (15.0)	0.724	10 (50.0)	10 (50.0)	0 (0.0)	0.[illegible]57	13 (65.0)	5 (25.0)	2 (10.0)	0.305
	No	120 (37.5)	147 (45.9)	53 (16.6)		113 (35.3)	137 (42.8)	70 (21.9)		160 (50.0)	136 (42.5)	24 (7.5)	

3′ end's VDR polymorphisms

Variables	Status	ApaI				BsmI				Tru[illegible]				TaqI				BglI			
		AA	Aa	aa	P	BB	Bb	bb	P	UU	U[illegible]	uu	P	TT	Tt	tt	P	GG	Gg	gg	P
Gender	Male	76 (37.4)	98 (48.3)	29 (14.3)	0.295	83 (40.9)	99 (48.8)	21 (10.3)	0.484	154 (75.9)	45 (22.2)	4 ([illegible])	0.127	102 (50.2)	72 (35.5)	29 (14.3)	0.519	137 (67.5)	54 (26.6)	12 (5.9)	0.425
	Female	62 (45.3)	55 (40.1)	20 (14.4)		58 (42.3)	70 (51.1)	9 (6.6)		108 (78.8)	22 (16.1)	7 (5.1)		70 (51.1)	53 (38.7)	14 (10.2)		83 (60.6)	44 (32.1)	10 (7.3)	
Fever	Yes	63 (32.6)	102 (52.8)	28 (14.5)	**0.001**	86 (44.6)	93 (48.2)	14 (7.3)	0.289	144 (74.[illegible])	[illegible] (22.8)	5 (2.6)	0.214	92 (47.7)	78 (40.4)	23 (11.9)	0.278	123 (63.7)	58 (30.1)	12 (6.2)	0.842
	No	75 (51.0)	51 (34.7)	21 (14.3)		55 (37.4)	76 (51.7)	16 (10.9)		118 ([illegible])	23 (15.6)	6 (4.1)		80 (54.4)	47 (32.0)	20 (13.6)		97 (66.0)	40 (27.2)	10 (6.8)	
Sore throat	Yes	48 (44.4)	44 (40.7)	16 (14.8)	0.539	43 (39.8)	56 (51.9)	9 (8.3)	0.[illegible]3	85 (78.7)	17 (15.7)	6 (5.6)	0.139	54 (50.0)	38 (35.2)	16 (14.8)	0.702	68 (63.0)	33 (30.6)	7 (6.5)	0.887
	No	90 (38.8)	109 (47.0)	33 (14.2)		98 (42.2)	113 (48.7)	[illegible] (9.1)		177 (76.3)	50 (21.6)	5 (2.2)		118 (50.9)	87 (37.5)	27 (11.6)		152 (65.5)	65 (28.0)	15 (6.5)	
Dry cough	Yes	75 (39.9)	85 (45.2)	28 (14.9)	0.941	80 (42.6)	94 (50.0)	[illegible] (7.4)	0.[illegible]8	137 (72.9)	44 (23.4)	7 (3.7)	0.123	95 (50.5)	65 (34.6)	28 (14.9)	0.328	119 (63.3)	57 (30.3)	12 (6.4)	0.794
	No	63 (41.4)	68 (44.7)	21 (13.8)		61 (40.1)	75 (4[illegible])	[illegible] (10.[illegible])		125 (82.2)	23 (15.1)	4 (2.6)		77 (50.7)	60 (39.5)	15 (9.9)		101 (66.4)	41 (27.0)	10 (6.6)	
Headache	Yes	26 (44.1)	21 (35.6)	12 (20.3)	0.187	26 (44.1)	[illegible] (47.[illegible])	[illegible] (8.5)	0.905	46 (78.0)	10 (16.9)	3 (5.1)	0.595	28 (47.5)	23 (39.0)	8 (13.6)	0.869	40 (67.8)	17 (28.8)	2 (3.4)	0.562
	No	112 (39.9)	132 (47.0)	37 (13.2)		115 ([illegible])	141 ([illegible])	25 (8.9)		216 (76.9)	57 (20.3)	8 (2.8)		144 (51.2)	102 (36.3)	35 (12.5)		180 (64.1)	81 (28.8)	20 (7.1)	
Shortness of breath	Yes	33 (36.7)	46 (51.1)	11 (12.2)	0.389	38 ([illegible])	42 (46.7)	10 (11.1)	0.616	61 (67.8)	24 (26.7)	5 (5.6)	**0.040**	44 (48.9)	35 (38.9)	11 (12.2)	0.888	64 (71.1)	21 (23.3)	5 (5.6)	0.330
	No	105 (42.0)	107 (42.8)	38 (14.4)		103 ([illegible])	127 (50.8)	20 (8.0)		201 (80.4)	43 (17.2)	6 (2.4)		128 (51.2)	90 (36.0)	32 (12.8)		156 (62.4)	77 (30.8)	17 (6.8)	
Diarrhea	Yes	15 (50.0)	12 (40.0)	[illegible] (10.0)	0.51[illegible]	11 (36.7)	15 (50.0)	4 (13.3)	0.624	22 (73.3)	7 (23.3)	1 (3.3)	0.869	15 (50.0)	9 (30.0)	6 (20.0)	0.403	22 (73.3)	8 (26.7)	0 (0.0)	0.278
	No	123 (39.7)	141 (45.5)	46 (14.8)		130 (41.9)	154 (49.7)	28 (8.4)		240 (77.4)	60 (19.4)	10 (3.2)		157 (50.6)	116 (37.4)	37 (11.9)		198 (63.9)	90 (29.0)	22 (7.1)	
Myalgia	Yes	34 (43.0)	38 (48.1)	7 (8.9)	0.276	30 (38.0)	39 (49.4)	10 (12.7)	0.364	63 (79.7)	16 (20.3)	0 (0.0)	0.179	43 (54.4)	29 (36.7)	7 (8.9)	0.480	56 (70.9)	17 (21.5)	6 (7.6)	0.257
	No	104 (39.8)	115 (44.1)	42 (16.1)		11 (42.5)	130 (49.8)	20 (7.7)		199 (76.2)	51 (19.5)	11 (4.2)		129 (49.4)	96 (36.8)	36 (13.8)		164 (62.8)	81 (31.0)	16 (6.1)	
Fatigue	Yes	18 (31.6)	31 (54.4)	8 (14.0)	0.257	25 (43.9)	30 (52.6)	2 (3.5)	0.301	40 (70.2)	13 (22.8)	4 (7.0)	0.151	23 (404)	27 (47.4)	7 (12.3)	0.172	40 (70.2)	14 (24.6)	3 (5.3)	0.637
	No	120 (42.4)	122 (43.1)	41 (14.5)		116 (41.0)	139 (49.1)	28 (9.9)		222 (78.4)	54 (19.1)	7 (2.5)		149 (52.7)	98 (34.6)	36 (12.7)		180 (63.6)	84 (29.7)	19 (6.7)	
Nausea	Yes	17 (43.6)	17 (43.6)	5 (12.8)	0.907	14 (35.9)	21 (53.8)	4 (10.3)	0.747	30 (76.9)	7 (17.9)	2 (5.1)	0.757	17 (43.6)	19 (48.7)	3 (7.7)	0.224	26 (66.7)	11 (28.2)	2 (5.1)	0.926
	No	121 (40.2)	136 (45.2)	44 (14.6)		127 (42.2)	148 (49.2)	26 (8.6)		232 (77.1)	60 (19.9)	9 (3.0)		155 (51.5)	106 (35.2)	40 (13.3)		194 (64.5)	87 (28.9)	20 (6.6)	
Vomiting	Yes	14 (48.3)	9 (31.0)	6 (20.7)	0.259	8 (27.6)	19 (65.5)	2 (6.9)	0.202	21 (72.4)	6 (20.7)	2 (6.9)	0.492	13 (44.8)	12 (41.4)	4 (13.8)	0.809	21 (72.4)	7 (24.1)	1 (3.4)	0.613
	No	124 (39.9)	144 (46.3)	43 (13.8)		133 (42.8)	150 (48.2)	28 (9.0)		241 (77.5)	61 (19.6)	9 (2.9)		159 (51.1)	113 (36.3)	39 (12.5)		199 (64.0)	91 (29.3)	21 (6.8)	
Parageusia	Yes	14 (36.8)	19 (50.0)	5 (13.2)	0.806	11 (28.9)	23 (60.5)	4 (10.5)	0.251	28 (73.7)	10 (26.3)	0 (0.0)	0.302	21 (55.3)	15 (39.5)	2 (5.3)	0.374	26 (68.4)	10 (26.3)	2 (5.3)	0.869
	No	124 (41.1)	134 (44.4)	44 (14.6)		130 (43.0)	146 (48.3)	26 (8.6)		234 (77.5)	57 (18.9)	11 (3.6)		151 (50.0)	110 (36.4)	41 (13.6)		194 (64.2)	88 (29.1)	20 (6.6)	
Hypertensio	Yes	35 (39.	42 (47.	12 (13.5)	0.883	34 (38.	46 (51.7)	9 (10.1)	0.729	60 (67.4)	26 (29.2)	3 (3.	**0.030**	43 (48.3)	35 (39.	11 (12.	0.841	58 (65.	26 (29.	5 (5.6)	0.930

n		3)	2)			2)						4)			3)	4)		2)	2)		
	No	103 (41.0)	111 (44.2)	37 (14.7)		107 (42.6)	123 (49.0)	21 (8.4)		202 (80.5)	41 (16.3)	8 (3.2)		129 (51.4)	90 (35.9)	32 (12.7)		162 (64.5)	72 (28.7)	17 (6.8)	
Diabetes	Yes	30 (39.5)	40 (52.6)	6 (7.9)	0.124	32 (42.1)	36 (47.4)	8 (10.5)	0.803	58 (76.3)	14 (18.4)	4 (5.3)	0.513	36 (47.4)	31 (40.8)	9 (11.8)	0.711	50 (65.8)	21 (27.6)	5 (6.6)	0.967
	No	108 (40.9)	113 (42.8)	43 (16.3)		109 (41.3)	133 (50.4)	22 (8.3)		204 (77.3)	53 (20.1)	7 (2.7)		136 (51.5)	94 (35.6)	34 (12.9)		170 (64.4)	77 (29.2)	17 (6.4)	
Asthma	Yes	11 (37.9)	9 (31.0)	9 (31.0)	**0.023**	12 (41.4)	12 (41.4)	5 (17.2)	0.224	24 (82.8)	4 (13.8)	1 (3.4)	0.704	16 (55.5)	10 (34.5)	3 (10.3)	0.857	14 (48.3)	11 (37.9)	4 (13.8)	0.088
	No	127 (40.8)	144 (46.3)	40 (12.9)		129 (41.5)	157 (50.5)	25 (8.0)		238 (76.5)	63 (20.3)	10 (3.2)		156 (50.2)	115 (37.0)	40 (12.9)		206 (66.2)	87 (28.0)	18 (5.8)	
Cardiovascular disease	Yes	15 (42.9)	16 (45.7)	4 (11.4)	0.863	14 (40.0)	16 (45.7)	9 (14.3)	0.481	25 (71.4)	9 (25.7)	1 (2.9)	0.640	15 (42.9)	13 (37.1)	7 (20.0)	0.345	25 (71.4)	8 (22.9)	2 (5.7)	0.674
	No	123 (40.3)	137 (44.9)	45 (14.8)		127 (41.6)	153 (50.2)	25 (8.2)		237 (77.7)	58 (19.0)	10 (3.3)		157 (51.5)	112 (36.7)	36 (11.8)		195 (63.9)	90 (29.5)	20 (6.6)	
Chronic renal disease	Yes	26 (40.6)	29 (45.3)	9 (14.1)	0.996	30 (46.9)	24 (37.5)	10 (15.6)	**0.029**	54 (84.4)	10 (15.6)	0 (0.0)	0.152	33 (51.6)	27 (42.2)	4 (6.2)	0.202	46 (71.9)	13 (20.3)	5 (7.8)	0.243
	No	112 (40.6)	124 (44.9)	40 (14.5)		111 (40.2)	145 (52.5)	20 (7.2)		208 (75.4)	57 (20.7)	11 (4.0)		139 (50.4)	98 (35.5)	39 (14.1)		174 (63.0)	85 (30.8)	17 (6.2)	
Malignancy	Yes	5 (25.0)	12 (60.0)	3 (15.0)	0.310	10 50.0 ()	8 (40.0)	2 (20.0)	0.667	15 (75.0)	4 (20.0)	1 (5.0)	0.897	6 ([illegible])	12 (60.0)	2 (10.0)	0.081	14 (70.0)	4 (20.0)	2 (10.0)	0.584
	No	133 (41.6)	141 (44.1)	46 (14.4)		131 (40.9)	161 (50.3)	28 (8.8)		247 (77.2)	63 (19.7)	10 (3.1)		[illegible] (51.9)	113 (35.3)	41 (12.8)		206 (64.4)	94 (29.4)	20 (6.2)	

Table 9. Significant association of VDR gene polymorphisms with some clinical symptom and comorbidities in COVID-19 patients

ApaI and fever			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*AA + Aa vs. aa*	0.954	0.98 (0.53- 1.81)
	aa vs. AA + Aa		1.02 (0.55- 1.89)
Recessive	*aa + Aa vs. AA*	**< 0.001**	2.15 (1.38- 3.34)
	AA vs. aa + Aa		0.47 (0.30- 0.73)
Overdominant	*Aa vs. AA + aa*	**< 0.001**	2.11 (1.36- 3.28)
	AA + aa vs. Aa		0.47 (0.31- 0.74)
Codominant	*aa vs. AA*	0.168	1.59 (0.82- 3.06)
	Aa vs. AA	**< 0.001**	2.38 (1.48- 3.83)
Allelic	*A vs. a*	**0.013**	0.67 (0.49- 0.92)
	a vs. A		1.49 (1.09- 2.04)
ApaI and asthma			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*AA + Aa vs. aa*	**0.011**	0.33 (0.14- 0.77)
	aa vs. AA + Aa		3.03 (1.30- 7.14)
Recessive	*aa + Aa vs. AA*	0.761	1.13 (0.52- 2.47)
	AA vs. aa + Aa		0.89 (0.41- 1.92)
Overdominant	*Aa vs. AA + aa*	0.119	0.52 (0.23- 1.18)
	AA + aa vs. Aa		1.92 (0.85- 4.35)
Codominant	*aa vs. AA*	**0.049**	2.60 (1.01- 6.72)
	Aa vs. AA	0.484	0.72 (0.29- 1.80)
Allelic	*A vs. a*	0.114	0.65 (0.38- 1.11)
	a vs. A		1.54 (0.90- 2.63)
BsmI and chronic renal disease			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*BB + Bb vs. bb*	**0.038**	0.42 (0.19- 0.95)
	bb vs. BB + Bb		2.38 (1.05- 5.26)
Recessive	*bb + Bb vs. BB*	0.331	0.76 (0.44- 1.32)
	BB vs. bb + Bb		1.32 (0.76- 2.27)
Overdominant	*Bb vs. BB + bb*	**0.032**	0.54 (0.31- 0.95)
	BB + bb vs. Bb		1.85 (1.05- 3.23)
Codominant	*bb vs. BB*	0.161	1.85 (0.78- 4.37)
	Bb vs. BB	0.104	0.61 (0.34- 1.11)
Allelic	*B vs. b*	0.853	0.96 (0.64- 1.44)
	b vs. B		1.04 (0.69- 1.56)
Tru9I and shortness of breath			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*UU + Uu vs. uu*	0.159	0.42 (0.12- 1.41)
	uu vs. UU + Uu		2.38 (0.71- 8.33)
Recessive	*uu + Uu vs. UU*	**0.016**	1.95 (1.14- 3.35)
	UU vs. uu + Uu		0.51 (0.30- 0.88)
Overdominant	*Uu vs. UU + uu*	0.055	1.75 (0.99- 3.10)
	UU + uu vs. Uu		0.57 (0.32- 1.01)
Codominant	*uu vs. UU*	0.105	2.75 (0.81- 9.31)
	Uu vs. UU	**0.038**	1.84 (1.03- 3.27)

Allelic	*U vs. u*	**0.008**	0.53 (0.33- 0.85)
	u vs. U		1.89 (1.18- 3.03)
Tru9I and hypertension			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*UU + Uu vs. uu*	0.933	0.94 (0.25- 3.64)
	uu vs. UU + Uu		1.06 (0.28- 4.00)
Recessive	*uu + Uu vs. UU*	**0.013**	1.99 (1.16- 3.43)
	UU vs. uu + Uu		0.50 (0.29- 0.86)
Overdominant	*Uu vs. UU + uu*	**0.010**	2.11 (1.20- 3.72)
	UU + uu vs. Uu		0.47 (0.27- 0.83)
Codominant	*uu vs. UU*	0.737	1.26 (0.32- 4.91)
	Uu vs. UU	**0.009**	2.14 (1.21- 3.77)
Allelic	*U vs. u*	**0.026**	0.58 (0.37- 0.94)
	u vs. U		1.72 (1.06- 2.70)
FokI and fever			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*FF + Ff vs. ff*	**0.017**	0.47 (0.25- 0.87)
	ff vs. FF + Ff		2.13 (1.15- 4.00)
Recessive	*ff + Ff vs. FF*	0.140	1.40 (0.90- 2.18)
	FF vs. ff + Ff		0.71 (0.46- 1.11)
Overdominant	*Ff vs. FF + ff*	0.711	0.92 (0.60- 1.42)
	ff + FF vs. Ff		1.09 (0.70- 1.67)
Codominant	*ff vs. FF*	**0.014**	2.35 (1.19- 4.62)
	Ff vs. FF	0.49[illegible]	1.18 (0.74- 1.89)
Allelic	*F vs. f*	**0.020**	0.69 (0.50- 0.94)
	f vs. F		1.45 (1.06- 2.00)
FokI and hypertension			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*FF + Ff vs. ff*	**0.016**	0.48 (0.26- 0.87)
	ff vs. FF + Ff		2.08 (1.15- 3.85)
Recessive	*ff + Ff vs. FF*	0.204	1.40 (0.83- 2.33)
	FF vs. ff + Ff		0.71 (0.43- 1.21)
Overdominant	*Ff vs. FF + ff*	0.560	0.87 (0.53- 1.41)
	ff + FF vs. Ff		1.15 (0.71- 1.89)
Codominant	*ff vs. FF*	**0.019**	2.27 (1.15- 4.48)
	Ff vs. FF	0.628	1.15 (0.66- 2.00)
Allelic	*F vs. f*	**0.028**	0.68 (0.48- 0.96)
	f vs. F		1.47 (1.04- 2.08)
CDX2 and headache			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*CC + Cc vs. cc*	**0.006**	0.42 (0.23- 0.78)
	cc vs. CC + Cc		2.38 (1.28- 4.35)
Recessive	*cc + Cc vs. CC*	0.485	1.24 (0.68- 2.25)
	CC vs. cc + Cc		0.81 (0.44- 1.47)
Overdominant	*Cc vs. CC + cc*	0.113	0.62 (0.35- 1.12)
	CC + cc vs. Cc		1.61 (0.89- 2.86)
Codominant	*cc vs. CC*	**0.031**	2.19 (1.07- 4.47)
	Cc vs. CC	0.668	0.86 (0.44- 1.70)
Allelic	*C vs. c*	**0.037**	0.66 (0.44- 0.98)
	c vs. C		1.51 (1.02- 2.27)
CDX2 and hypertension			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*CC + Cc vs. cc*	**0.001**	0.40 (0.23- 0.70)
	cc vs. CC + Cc		2.50 (1.43- 4.35)
Recessive	*cc + Cc vs. CC*	0.282	1.33 (0.79- 2.22)
	CC vs. cc + Cc		0.75 (0.45- 1.27)
Overdominant	*Cc vs. CC + cc*	0.108	0.66 (0.40- 1.09)
	CC + cc vs. Cc		1.52 (0.92- 2.50)
Codominant	*cc vs. CC*	**0.007**	2.40 (1.27- 4.53)
	Cc vs. CC	0.845	0.94 (0.53- 1.68)
Allelic	*C vs. c*	**0.009**	0.63 (0.45- 0.89)
	c vs. C		1.59 (1.12- 2.22)
CDX2 and diabetes			
Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*CC + Cc vs. cc*	**0.008**	0.46 (0.26- 0.82)
	cc vs. CC + Cc		2.17 (1.22- 3.85)
Recessive	*cc + Cc vs. CC*	**0.044**	1.79 (1.06- 3.16)
	CC vs. cc + Cc		0.56 (0.32- 0.94)
Overdominant	*Cc vs. CC + cc*	0.823	0.94 (0.56- 1.58)
	CC + cc vs. Cc		1.06 (0.63- 1.79)
Codominant	*cc vs. CC*	**0.005**	2.69 (1.35- 5.35)
	Cc vs. CC	0.254	1.43 (0.77- 2.66)
Allelic	*C vs. c*	**0.003**	0.58 (0.40- 0.84)
	c vs. C		1.72 (1.19- 2.50)
EcoRV and diabetes			

Genetic models		P- value	Odds ratio (95 % CI)
Dominant	*EE + Ee vs. ee*	**0.014**	0.36 (0.16- 0.81)
	ee vs. EE + Ee		2.78 (1.24- 6.25)
Recessive	*ee + Ee vs. EE*	**< 0.001**	3.86 (2.19- 6.80)
	EE vs. ee + Ee		0.26 (0.15- 0.46)
Overdominant	*Ee vs. EE + ee*	**< 0.001**	2.54 (1.51- 4.28)
	EE + ee vs. Ee		0.39 (0.23- 0.66)
Codominant	*ee vs. EE*	**< 0.001**	5.61 (2.27- 13.89)
	Ee vs. EE	**< 0.001**	3.59 (2.00- 6.44)
Allelic	*E vs. e*	**< 0.001**	0.40 (0.27- 0.58)
	e vs. E		2.50 (1.72- 3.70)

Highlights

- Growing evidence indicated the critical impacts of vitamin D (VD) in prognosis of COVID-19 patients.
- Significant associations were disclosed for some of the SNPs with severity, signs, symptoms, and co-existing pathologic conditions.
- VDR gene polymorphisms might thus allow the prioritization of those at greater risk for COVID-19.