INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the Coronaviridae family, causes respiratory and gastrointestinal infections. The World Health Organization named the disease caused by this virus COVID-19, which is an acronym for ‘coronavirus disease 2019’, while the agent was named SARS-CoV-2 due to its similarity to SARS-CoV (Bassetti et al., 2020). Since the science and medical community has not faced such a widespread epidemic before, local experiences come to the forefront of managing this situation (Rombolà et al., 2020). Patients with severe symptoms who require hospitalization for SARS-CoV-2 infection include men, old people, smokers, patients with obesity and those with common comorbidities such as cardiovascular diseases, diabetes and chronic...
lung disease (Yang et al., 2020). However, to reduce the mortality rate of COVID-19, further investigation is still needed to find effective indicators for assessing the severity and clinical progression of the disease. Some of the patients show only mild fever, cough or muscle soreness, while some patients’ conditions deteriorate in the later stages and result in death due to acute respiratory distress syndrome (ARDS) and multiple organ failure (Guo et al., 2020). Huang et al. (2020) reported the clinical features and cytokine profile of patients with COVID-19 in Wuhan, China, and suggested that a cytokine storm could be associated with the severity of the disease. In addition, Xu et al. (2020) examined biopsy samples from the deceased, and interstitial mononuclear inflammatory infiltrates predominated by lymphocytes were seen in both lungs. The SARS-CoV-2 infection causes a sequential release of specific cytokines that cause significant damage to the pulmonary epithelium, resulting in ARDS, sepsis and organ failure (Mehta et al., 2020).

In Huang et al.’s study, initial plasma IL1RA, IL1B, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα and vascular endothelial growth factor (VEGF) concentrations were higher in patients with COVID-19 than in healthy controls. In addition, of a total of 81,385 cases of COVID-19 reported by the Chinese Center for Disease Control and Prevention, 81% were mild, 14% severe and 5% critical (Wu & McGoogan, 2020). Thus, genetic variations in cytokines and their receptors could play an important role in the progression or severity of COVID-19 infection.

The vascular structure in the respiratory system plays an important role in maintaining the physiological functions of expansive capacity and major plasticity. Various pathologic conditions, including COVID-19, increase the permeability of vascular endothelial cells, expression of adhesion molecules, migration and proliferation of endothelial cells, and infiltration of inflammatory cells (McDonald, 2001). VEGF is considered the most important factor (Riedel et al., 2002) because of the increase in the inflammatory process and serum levels of VEGF in patients with COVID-19. VEGF produces this effect by binding to VEGF receptor type 1 (VEGFR1) or VEGF receptor type 2 (VEGFR2), which have tyrosine kinase activity (Shibuya & Claesson-Welsh, 2006). VEGF-R2 is regarded as the main signalling receptor for VEGF bioactivity (angiogenesis, proliferation and permeability) and can cause proliferation in cells lacking VEGFR1 (Carmeliet et al., 2001). Downstream signal transduction pathways are triggered by VEGFR2 receptor kinase activity—which promotes the proliferation, migration and differentiation of endothelial cells and enhances the permeability of the microvasculature. Alveolar apoptosis and emphysema occur when VEGF activity is inhibited by VEGFR2 in rats (Kasahara et al., 2000).

Single nucleotide polymorphisms (SNPs) can be located in other gene regions—such as 5′- or 3′-UTRs, introns or promoters and the exonic region. Genetic variations in 3′-UTRs can modify gene expression via miRNA binding, protein–mRNA interactions, gene expression disruption and polyadenylation; therefore, SNPs in 3′-UTRs are very important and arouse the interest of researchers. Furthermore, it has been shown that SNPs in 3′-UTRs can affect miRNA functions by changing thermodynamic properties of the hybridization site and the secondary structure of 3′-UTRs, lowering binding yield, exchanging miRNA recognition elements and, probably, creating new binding sites or enhancing binding efficiency between the target site and miRNA (Schwerk & Savan, 2015; Steri et al., 2018). These 3′-UTR-located SNPs have been found to be useful tools for the development of medicine, assessment of disease susceptibility and monitoring of the clinical symptoms of patients in several studies (Ding et al., 2018).

There are a significant number of SNPs in genes encoding cytokines that are high in patients with COVID-19, and the process of verifying the potential relationship between SNPs and diseases in the laboratory is costly and, most importantly, time-consuming. In silico analyses allow for narrowing the regions of potential SNP targets for experimental validation. Using bioinformatic tools, the present study aimed to determine the genetic variations in cytokines and cytokine receptors that are possibly related to COVID-19 pathogenesis.

## 2 | MATERIALS AND METHODS

The SNPs for genes coding the cytokines and their receptors that were elevated in patients with COVID-19 were chosen from the dbSNP database, which is available on the National Biotechnology Information Center website (http://www.ncbi.nlm.nih.gov/SNP). Variant analysis was carried out for the SNPs (synonymous and nonsynonymous) in the coding region and the untranslated regions with MAF > 0.15. We analysed the missense SNPs in 3 cytokine genes and 10 cytokine receptor genes using sorting intolerant from tolerant (SIFT) to predict the deleterious and tolerated SNPs (https://sift.bii.a-star.edu.sg/www/SIFT_dbSNP.html). SIFT uses sequence homology or physical properties to predict the effects of amino acid substitution on protein function and, hence, potential alteration on phenotype (Kumar et al., 2009).

Further analysis was conducted for the deleterious SNPs identified with SIFT by PolyPhen and I-Mutant2.0 database. PolyPhen prediction is based on a series of features—including phylogenetic, structural and sequence annotation information characterizing a substitution. PolyPhen classifies the SNPs as ‘probably damaging’, ‘possibly damaging’ or ‘benign’ (Ramensky et al., 2002). For the prediction of the missense SNP impact on the stability of the protein, the I-Mutant2.0 database was used (Capriotti et al., 2005). Furthermore, miRNA binding efficiency was also affected by the SNPs in the 3′-UTR. Therefore, miRSNP was used to predict whether the SNPs affected the miRNA binding efficiency for the cytokine genes and receptors.

## 3 | RESULTS

The number of the synonymous and nonsynonymous coding SNPs and the SNPs from the untranslated regions of the genes coding
cytokines and their receptors that were possibly related to COVID-19 pathogenesis is listed in Table 1. SIFT was used for the functional significance analysis of the SNPs. The prediction results of the missense SNPs by SIFT are presented in Table 2. One SNP in the VEGFR2 gene was predicted as deleterious, and 13 SNPs were predicted as ‘tolerable’ by SIFT. The other SNP tools such as PolyPhen and I-Mutant2.0 were used for further analysis of this deleterious SNP. PolyPhen predicted that as benign, where the I-Mutant2.0 prediction showed decreased stability (Table 2).

The possible alterations caused by the 3′-UTR SNPs were investigated for the miRNA binding efficiency in the listed genes that were suggested to have potential roles in COVID-19. We predicted that the 27 SNPs affected the miRNA binding for the cytokine receptor genes and 10 SNPs for cytokine genes by in silico analysis.

Table 1: Number of the synonymous and nonsynonymous coding SNPs and the SNPs from the untranslated regions and intron of the genes coding cytokines and cytokine receptors that were high plasma concentrations in COVID-19 patients

| Gene name | 3′- UTR | 5′- UTR | Intron upstream and downstream transcript variant | Synonymous variant | Missense variant |
|-----------|---------|---------|---------------------------------------------------|-------------------|-----------------|
| **Cytokine genes** |
| CCL2      | 1       | 2       | 1                                                 |                  |                 |
| CCL3      | 2       | 7       | 1                                                 |                  |                 |
| CCL4      | 29      | 1       | 2                                                 |                  |                 |
| CSF2      | 8       | 1       | 1                                                 |                  |                 |
| CSF3      | 7       | 1       | 1                                                 |                  |                 |
| CXCL8     | 6       | 1       | 1                                                 |                  |                 |
| CXCL10    | 17      | 1       | 1                                                 |                  |                 |
| IFNG      | 9       | 1       | 1                                                 |                  |                 |
| IL1B      | 10      | 1       | 1                                                 |                  |                 |
| IL1RN     | 143     | 2       | 1                                                 |                  |                 |
| IL7       | 109     | 1       | 1                                                 |                  |                 |
| IL9       | 6       | 1       | 1                                                 |                  |                 |
| IL10      | 12      | 1       | 1                                                 |                  |                 |
| PDGFB     | 63      | 1       | 1                                                 |                  |                 |
| TNF       | 2       | 1       | 1                                                 |                  |                 |
| VEGFA     | 40      | 1       | 1                                                 |                  |                 |
| **Cytokine receptor genes** |
| CCR1      | 4       | 1       | 1                                                 |                  |                 |
| CCR2      | 15      | 1       | 1                                                 |                  |                 |
| CCR4      | 5       | 1       | 1                                                 |                  |                 |
| CCR5      | 14      | 1       | 1                                                 |                  |                 |
| CSF2RA    | 420     | 1       | 1                                                 |                  |                 |
| CSF3R     | 22      | 1       | 1                                                 |                  |                 |
| CXCR1     | 1       | 1       | 1                                                 |                  |                 |
| CXCR2     | 15      | 1       | 1                                                 |                  |                 |
| CXCR3     | 2       | 1       | 1                                                 |                  |                 |
| FLT1      | 254     | 1       | 1                                                 |                  |                 |
| IFNGR1    | 16      | 1       | 1                                                 |                  |                 |
| IFNGR2    | 59      | 1       | 1                                                 |                  |                 |
| IL1R1     | 260     | 1       | 1                                                 |                  |                 |
| IL1R2     | 110     | 1       | 1                                                 |                  |                 |
| IL7R      | 53      | 1       | 1                                                 |                  |                 |
| IL9R      | 30      | 1       | 1                                                 |                  |                 |
| IL10RA    | 17      | 1       | 1                                                 |                  |                 |
| IL10RB    | 85      | 1       | 1                                                 |                  |                 |
| KDR       | 89      | 1       | 1                                                 |                  |                 |
| TNFRSF1A  | 22      | 1       | 1                                                 |                  |                 |
| TNFRSF1B  | 47      | 1       | 1                                                 |                  |                 |
TABLE 2  SIFT, PolyPhen-2 and I-Mutant-2.0 results of missense SNPs of genes encoding the cytokines and cytokine receptors that was elevated in COVID-19 patients

| Gene name       | Gene ID     | SNP       | Allele change | Amino acid change | SIFT prediction | Polyphen-2 prediction | I-Mutant-2.0 prediction |
|-----------------|-------------|-----------|---------------|-------------------|-----------------|-----------------------|------------------------|
| Cytokine genes  |             |           |               |                   |                 |                       |                        |
| CCL4            | ENSG00000129277 | rs1049807 | A/G           | N41S E79E         | Tolerated       |                       |                        |
| CCL4            | ENSG00000129277 | rs1719152 | T/A           | S80T N41K         | Tolerated       |                       |                        |
| CSF2            | ENSG00000164400 | rs25882   | T/C           | I117T             | Tolerated       |                       |                        |
| Cytokine receptor genes |       |           |               |                   |                 |                       |                        |
| CCR2            | ENSG00000121807 | rs1799864 | G/A           | V64I              | Tolerated       |                       |                        |
| IFNGR2          | ENSG00000159128 | rs9808753 | A/G           | Q83R, Q64R        | Tolerated       |                       |                        |
| IL7R            | ENSG00000168685 | rs1494558 | T/C           | I66T              | Tolerated       |                       |                        |
| IL7R            | ENSG00000168685 | rs6897932 | C/T           | T244I             | Tolerated       |                       |                        |
| IL7R            | ENSG00000168685 | rs1494555 | G/A           | V138I             | Tolerated       |                       |                        |
| IL10RA          | ENSG00000110324 | rs2229113 | A/G           | R351G R331G R202G | Tolerated       |                       |                        |
| TNFRSF1B        | ENSG00000028137 | rs1061622 | T/G           | M196R             | Tolerated       |                       |                        |
| IL10RB          | ENSG00000243646 | rs2834167 | A/G           | K47E              | Tolerated       |                       |                        |
| KDR             | ENSG00000128052 | rs1870377 | T/A           | Q472H             | Deleterious     | Benign                | Decrease stability     |
| KDR             | ENSG00000128052 | rs2305948 | C/T           | V297I             | Tolerated       |                       |                        |

4 | DISCUSSION

We determined the genetic variations of genes coding cytokines and receptors in relation to COVID-19 by using bioinformatic tools. There are four missense SNPs in genes encoding cytokines that had high plasma concentrations in patients with COVID-19. But SIFT analysis predicted that these variations are tolerable and not expected to affect the protein function. However, of the 10 missense polymorphisms found in genes coding the receptors, VEGFR2 gene Q472H (rs1870377) polymorphism was predicted to have a deleterious effect by SIFT and I-Mutant2.0 prediction database predicted that this polymorphism decreased the stability of the protein.

The VEGFR2 gene consists of 26 exons, is located in 4q11–q12 and encodes 1,356 amino acids. Missense substitution (c.1416A > T) causes Q472H change in the fifth extracellular Ig-like motifs (Glubb et al., 2011). VEGF has an important function in suppressing the apoptosis cascade and reducing oedema formation by decreasing the increased endothelial permeability following the intratracheal application of inflammatory stimuli. Koh et al. (2007) reported that VEGF is a major protective factor for the damaged lung during the progression of ARDS. The decrease in VEGFR2 function due to the rs1870377 polymorphism may be the reason for vascular dysfunction—including impaired endothelial cell survival, endothelial cell damage and abnormal vascular repair, contributing to the progression of COVID-19 and the pathogenesis. However, there are no sequence data for rs1870377 variants from patients with COVID-19 and the frequency of this variant is close to 50% in East Asian, Vietnamese and Korean populations. This limits the impact of our findings.

Gene regulation has an essential role in host defence against pathogens, and its dysregulation has been demonstrated in different infectious diseases or disease progression (Chandan et al., 2020). 3′-UTR polymorphism in genes encoding cytokines or their receptors was found in higher levels in patients with COVID-19 (Table 3). The effect of SNPs on miRNA binding efficiency and the variant that is responsible for the described effect is shown in Table 3. Among these polymorphisms, CXCR2 rs1126579, TNFRSF1B rs1061624 and IL10RB rs8178562 are particularly remarkable because these SNPs would break the miRNA-mRNA binding sites for miR-516a-3p, miR-720 and miR-328, respectively. It has been suggested that the main cause of lung injury during a response to SARS-CoV-2 is an increase in these pro-inflammatory cytokines and the dysregulation of the immune response.

Narożna et al. (2017) reported that miR-328 represents a potent modifier of the complex process of wound repair in bronchial epithelial cells and inhibition of miR-328 interrupts the repair process. In addition, Wu et al. (2019) demonstrated that miR-516a-3p expression knockdown could inhibit cell proliferation, invasion, migration and wound repair but promote apoptosis in lung adenocarcinoma cells. Also, previous studies have reported that miR-328 plays important role in regulating the expression of genes associated with cell–cell interactions, transport across the membranes (Li et al., 2011), migration and cell adhesion (Ishimoto et al., 2014), and calcium-dependent processes such as cell division, cell motility and cell death (Lu et al., 2010). Hence, the increased expression of these
| Gene        | SNP      | Allele | Effect          |
|------------|----------|--------|-----------------|
|            |          |        | Decrease | Enhance | Create | Break |
| Cytokine genes |          |        |           |         |         |       |
| CCL2       | rs13900  | C      | hsa-miR-3163 | hsa-miR-374a-5p | hsa-miR-4761-5p | hsa-miR-624-3p |
|            | rs8951   | G      | hsa-miR-5002-3p | hsa-miR-4672 | hsa-miR-3929 | hsa-miR-4419b |
|            | rs1063340| G      |            |           | hsa-miR-3179 | hsa-miR-1292 |
| CCL3       | rs2827   | C      | hsa-miR-3653 | hsa-miR-3658 | hsa-miR-500-3p | hsa-miR-5586-5p |
|            | rs1042658| C      |            |           | hsa-miR-3179 | hsa-miR-1292 |
| IL8        | rs1126647| A      | hsa-miR-944  | hsa-miR-944  | hsa-miR-145-3p | hsa-miR-548ad |
| CXCL10     | rs3921   | C      | hsa-miR-5002-5p | hsa-miR-145-3p | hsa-miR-1538 | hsa-miR-591 |
| VEGFA      | rs34836828| Deletion |            | hsa-miR-145-3p | hsa-miR-1538 | hsa-miR-591 |
|            | rs3025040| C      |            | hsa-miR-145-3p | hsa-miR-1538 | hsa-miR-591 |
|            | rs10434  | A      | hsa-miR-4727-5p | hsa-miR-3677-5p | hsa-miR-3545-5p | hsa-miR-660-3p |
| Cytokine receptor genes |          |        |           |         |         |       |
| CCR2       | rs743660  | A      | hsa-miR-4786-3p | hsa-miR-4786-3p | hsa-miR-31133 | hsa-miR-31133 |
| CCR5       | rs746492  | T      | hsa-miR-5007-3p | hsa-miR-5007-3p | hsa-miR-5007-3p | hsa-miR-5007-3p |
| CXCR2      | rs1126579 | C      | hsa-miR-5193  | hsa-miR-5193  | hsa-miR-516a-3p | hsa-miR-516b-3p |
|            | rs1126580 | A      | hsa-miR-4524b-3p | hsa-miR-5096 | hsa-miR-5096 | hsa-miR-5096 |
| FLT1       | rs2296283 | C      | hsa-miR-3943  | hsa-miR-3943  | hsa-miR-1538 | hsa-miR-1538 |
|            | rs2296284 | C      | hsa-miR-3943  | hsa-miR-3943  | hsa-miR-4731-5p | hsa-miR-4731-5p |
|            | rs10434   | A      | hsa-miR-4727-5p | hsa-miR-3677-5p | hsa-miR-3545-5p | hsa-miR-660-3p |
|            | rs3209052 | A      | hsa-miR-4789-3p | hsa-miR-4789-3p | hsa-miR-3133 | hsa-miR-3133 |
|            | rs3751397 | T      | hsa-miR-3662  | hsa-miR-3662  | hsa-miR-548a-3p | hsa-miR-548a-3p |
|            | rs17086617| G      | hsa-miR-223-5p | hsa-miR-223-5p | hsa-miR-4446-5p | hsa-miR-4446-5p |

(Continues)
miRNAs is inevitable to repair lung damage that is associated with COVID-19. We can speculate that high expression of miR-516a-3p and miR-328, as a result of the repair of the lung damage, by reducing the cytokine levels, might be obstructed by the related SNPs. However, further studies are needed to determine the role of these miRNAs in COVID-19 pathogenesis.

The total number of NK and CD8+ T cells decreased markedly in patients with SARS-CoV-2 infection (Zheng et al., 2020). miR-720 regulates TCR-mediated proliferation of primary human CD8+ T cells and has an important role in immune regulation (Wang et al., 2015). The upregulation of miR-720 in CD8+ T cells may play a role in the progression of COVID-19. It was also found in our study that rs1061624 polymorphism in the TNFRSF1B gene disturbed the miR-720 regulator effect on TNFRSF1B expression. Therefore, this is a valid candidate for further study on the pathogenesis and progression of COVID-19.

In conclusion, our analysis, using the bioinformatic approach, showed that VEGFR2 rs1870377 polymorphism comes into prominence according to SIFT and the I-Mutant2.0 database. Also, CXCR2 rs1126579, TNFRSF1B rs1061624 and IL10RB rs8178562 attracted attention because it was predicted that these SNPs could break the miRNA-mRNA binding sites for miR-516a-3p, miR-720 and miR-328, which are important miRNAs in immune regulation and repair of damage in the lungs.
CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

Güneş Çakmak Genç carried out the literature review, while Sevim Karakaş Çelik conducted the bioinformatic analyses. Güneş Çakmak Genç, Sevim Karakaş Çelik and Ahmet Dursun performed the evaluation and discussion of the results.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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