University of Thi-Qar Journal of Science (UTJsci)
E-ISSN: 2709-0256, P-ISSN: 1991-8690, Vol. 12, No.1,Jun. 2025

The Association between COVID-19 Infection and both rs34224237IL-6 and rs1800871 IL-10 Gene Polymorphisms

Abdulaziz Salih Abdulaziz*[1a]

[1]*Department of Microbiology, College of Veterinary Medicine, University of Shatrah, Thi-Qar, Iraq.*

[a*]Corresponding author: Abdulaziz@shu.edu.iq

Received:2024-09-22, Revised: 2024-10-31, Accepted:2024-12-10, Published: 2025-06-16

***Abstract*— Investigate the polymorphism of the IL-6 and IL-10 genes in COVID-19 patients was the goal of this study. Fifty COVID-19 patients and 50 samples as control used in this study on 7/12/2023. The results recorded that a significantly relation (P= 0.03) of rs34224237 (AAAAAAAAA SNP) was detected in the studied samples (COVID-19) and control, that variation of A nucleotide in position 22726806. While, the results of this study showed a high significantly relationship (P= 0.0007) of rs1800871 (A>G) in position 206773289. In conclusion, This study showed the polymorphism of IL-10 (rs1800871, A>G SNP) was a highly significantly associated with COVID-19 infection, which could be employed as a diagnostic marker for COVID-19 infections.**

***Keywords*— IL-6, IL-10, rs34224237, rs1800871, Polymorphism, COVID-19.**

I. INTRODUCTION

The severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) began to spread toward the end of 2019 and was a huge global outbreak that affected public health. [1] .The coronavirus disease that began in 2019(COVID-19) was caused by SARS-CoV-2.The disease's clinical manifestation varies from mild to severe, with respiratory distress occurring in up to 14% of cases and multi-organ failure and potentially fatal respiratory failure in up to 5% of cases[2]. Numerous investigations have demonstrated that COVID-19 is linked to immunodeficiency and hyper-inflammation, exemplified by cytokine storm [3].

Among these cytokines was the interleukin 6 IL6 , which can be used as a prognostic marker because of its capacity to differentiate between moderate and severe illness [4]. It was also found to be substantially correlated with the severity of the disease. Moreover, host variables like comorbidities, age, and IL-6 gene polymorphisms can contribute to that variation [5]. The (IL-6 gene) is found on chromosome 7 and has been found to include a significant number of polymorphisms, particularly in the non-coding promoter region. According to [6] , these polymorphisms significantly impact gene expression.

Cytokines and SNPs such as IL-17A and IL-6 gene polymorphism increased the risk of severe COVID-19 in patients. These alterations primarily impact gene expression, turn triggering a cytokine storm that adversely affects immune cells [7]. According to [8], Macrophages, mast cells, natural killer (NK) cells, neutrophils T and B cells are examples of innate and adaptive immunity cells that produce IL-10 a pleiotropic and immunosuppressive, and potent anti-inflammatory cytokine.

In COVID-19 patients, the main reasons for death were damage to vital organs, severe pneumonia, and the involvement of numerous pro-inflammatory mediators. Trials using randomized placebo-controlled designs have not yet demonstrated the effectiveness of blocking IL-6,IL-1,or GM-CSF in lowering death rates among COVID-19 patients [9]. This gene is an anti-inflammatory cytokine that ,by inhibiting the synthesis of proinflammatory cytokines, hindering the immune system from mounting a defense against infections [10]. It is generated by T cells and myeloid cells and is located on the long arm of chromosome-1(1q31–1q32)locus[11].Similarly, peripheral blood samples from COVID-19 patients had been shown to have a lower lymphocyte count and a higher level of inflammatory cytokines [12].

A more profound comprehension of the clinical aspects was desperately needed, as COVID-19 was spreading quickly ,and the fatality rate for severe cases was significant. This understanding could aid In the identifying of trustworthy markers for monitoring inflammation as the disease progresses. The storm of inflammatory factors might be the primary cause of the rapid course of disease and the poor response to treatment, according to prior pertinent research on the current therapy experience and pneumonia with severe type COVID-19 [12,13]. Nonetheless, a subset of individuals exhibiting respiratory failure due to severe illness had demonstrated a high death rate [14]. Currently, monitoring severe COVID-19 cases primarily depends on clinical presentation observation because there is no accurate marker or effective antiviral therapy [14] [15].According to previous research, infections with extremely pathogenic coronaviruses, including SARS and MERS, were often associated with lymphocytopenia and inflammatory cytokine storm, which were thought to be related to the severity of the illness [12]. The study aimed to

https://doi.org/10.32792/utq/utjsci/v12i1.1305

investigate the function of IL-6 gene (rs34224237) and IL-10 gene (rs1800871) polymorphisms in COVID-19 patients.

II. Materials and Methods

The participants in this study were 50 patients at Al-Hussain Teaching Hospital, in Thi-Qar province, Iraq, who were diagnosed with COVID-19 by RT-PCR between January and August of 2022. The control group consisted of 50 healthy individuals. Individuals with respiratory symptoms younger than ten years old were eligible for inclusion. None of the patients had autoimmune disorders, immunosuppressive medications, or compromised immune systems. Using a SARS-CoV-2 RNA-RT-PCR assay on nasopharyngeal swab samples from the patients, COVID-19 was verified in those individuals. The selection of samples was based on a respiratory rate (fewer than 24 breaths per minute). Following patient consent,2mL of peripheral blood samples were taken from each patient, and placed in EDTA-coated vials.

a) DNA Extraction

With a human gSYNCTM DNA extraction Kit, genomic DNA was extracted from whole blood samples by the manufacturer's instructions.

b) Primers

Primers sequences were used in the present study are included *IL-6* gene as follows,F:5´GGTAGTGCTCACCATGACCCC3´, R: 5´ACACTGGAAATGCCCTCCATC3´ with molecular size (781bp); while *IL-10* gene, F:5´CCCTTTCTGCCCTGAACCAA3´, R: 5´GAGGCTAGCGCTAAGAAGCA3´ with product size (708bp) (in this study).

c) PCR Detection of Target Genes

Amplification 100 samples for each gene of the *IL-10* and *IL-6* genes were done using primers described above. The reaction tubes had a final volume of 20µl, which was made up of 12.5µl of Geneaid/Taiwan Master Mix, 1µl of each gene-specific forward and reverse primer,2µl of DNA-template, and nuclease free water to finish the volume. The primers for the IL-10 and IL-6 genes were denatured at 95 ◦C for 5 min, then there were 30 cycles of denaturation at 94 ◦C for 30 Sec, an annealing temperature of thirty seconds at 57.4 ◦C for IL-10 and 54 ◦C for IL-6,and a final extension step at 72 ◦C for 5 min. By using (2%)gel electrophoresis, the specificity of the PCR fragments containing 708 bp and 781 bp of interleukin-6(IL-6)and interleukin-10(IL-10)gene polymorphisms, respectively, was examined.

d) DNA Sequencing

For the Sanger sequencing method, 100 PCR product samples (forward) for the IL-6 and IL-10 genes were sequenced using the ABI3730XL_automated DNA sequencing machine (Macrogen Corporation, Korea). The genotypes of these samples were then determined by aligning them with reference sequences found in the Gene Bank using the Geneious software version 10.2.2.

e) Statistical Analysis

The IBM SPSS software package, version 22, was used for all statistical analyses. The genotype and allele frequencies for the IL-6 and IL-10 genes were compared between the cohorts of healthy individuals and COVID-19 patients using the Chi-square test. In addition, logistic regression was used to determine the Hardy–Weinberg equilibrium, odds ratios (ORs), and 95% confidence intervals (CIs) in order to assess the importance of these variations. P-values of less than 0.05 were regarded as statistically significant.

III. Results

a) DNA Extraction

All samples showed DNA extracted positive results as show in Figure 1

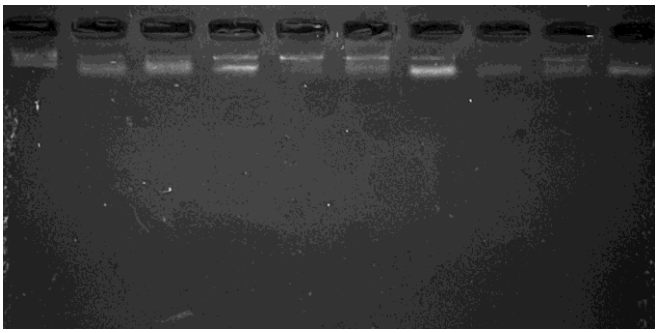

Fig 1**:** Total genomic (DNA) extraction

b) The distribution of COVID-19 patients depending age groups

The current study comprised of patients and a control group, each of individuals in different age ranges, as shown in Table (1).

When compared to the other age categories, the age group of 52–70 years had the largest percentage of people (36%) who were infected with COVID-19, followed by the age group of 42–51 years (22%); the age group of 22–31 years had the lowest percentage. The data showed significant differences (P≤ 0.05) between the age categories of COVID-19 patients.

Table1: Distribution of studied groups to the age

Age group	Patients group		P.Value
	NO	%	
13 – 21	7	14%	0.013
22 – 31	5	10%	
32 – 41	9	18%	
42 – 51	11	22%	
52-70	18	36%	
Total	50	100 %	
	X^2 = 12.5 , df = 4		

In the COVID-19 patients group, (64%) were male, while (36%) were female. While 70% of the members were male and 30% were female in the control group, Table (2) indicates that there is statistically significant variation in the

gender distribution among the study groups, with a P-value (0.0051)

Table 2: Distribution of studied groups to the sex

Sex	Patients group		P.Value
	NO	%	
Male	32	64%	0.0051
Female	18	36%	
Total	50	100 %	
		X^2 = 7.84 , df = 1	

c) PCR Results for IL-6 and IL-10 Genes.

Results of the PCR assay for the *IL-10* gene in COVID-19 and control samples revealed that complete samples (100%) harbored this gene. Also, the percentage of IL-6 gene was (100%) in both COVID-19 and the control samples. The size of IL-10 and L-6 genes which were approximately 781bp and 708bp, respectively showed in figure 2

Table

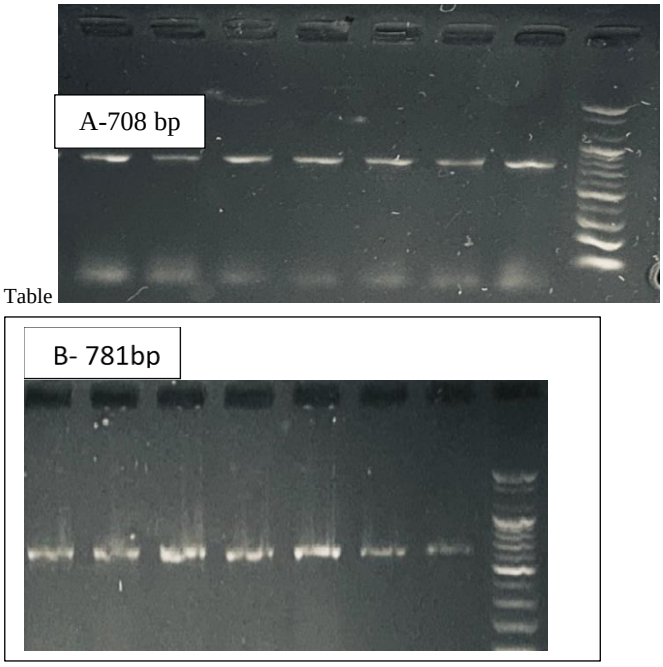

Fig 2: Gel electrophoresis of (A)L-6 and (B) IL-10 genes ,1.5 % agaros at 70 votes

d) Sequencing Analysis

1) IL-6 Gene Polymorphism

Following NCBI n BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi), the sequencing processes revealed an exact identity of the already amplified genomic region. The amplified samples and the planned reference target sequences, which partially cover the IL-6and IL-10 genes, showed 100% sequence homology according to this engine. Through contrasting the returned DNA sequences of the interleukin-6(IL-6)and interleukin-10(IL-10)genes(Gen Bank acc. NC_000007.14; NC_000001.11) with the observed DNA variations of the samples under analysis at the time.

e) Hardy-Weinberg equilibrium

The Hardy-Weinberg Equilibrium (HWE) is a notion that, without perturbing influences, states that genetic variation in a population will not change from generation to generation. The rs34224237 AAAAAAAA/AAAAAAAAA/AAAAAAAAAA SNP genotype and allele frequency of IL-6 are displayed in tables (3), (4), and (5) in order to compute HWE. The study's findings support HWE, with a non-significantly high (P=0.03) result for rs34224237. The desired high-frequency (AAAAAAAAA SNP), which is a variant of the A nucleotide in position 22726806 of the amplified PCR fragments, namely AAAAAAAAA, was found in the samples under investigation (COVID-19 and control).

The allele and genotype frequency of IL-10, rs1800871, an A>G SNP, are displayed in tables (8), (9) , and (10) and are used to determine the HWE of the IL-10 gene. The study's findings support HWE, with rs1800871 showing a significant outcome (P=0.0007). Most samples (COVID-19 and control) showed the intended high-frequency genotype (GG), which is those with the nucleotide variant at position 206773289 of the amplified PCR fragments (A>G SNP).

The polymorphic patterns that exist are AAAAAAAA, AAAAAAAAA, and AAAAAAAAAA. While the AAAAAAAA pattern was seen in both cases (14/50) and controls (6/50), the AAAAAAAAA status was found in the majority of samples in cases (26/50) and controls (38/50). As shown in Table (3), it is noteworthy that the AAAAAAAAA pattern was found in the cases (10/50) and control (12/50) of rs34224237.

Table3: Genotype frequency of rs34224237 of IL6 among COVID 19 and control

rs34224237	Case: 50	Control: 50	OR	P- value
AAAAAAAA	14	6	1.0	----
AAAAAAAAA	26	32	2.8	0.4
AAAAAAAAAA	10	12	2.8	0.6

Table (4) shows a statistically significant link between allele frequency of IL-6, rs34224237 SNP, and the development of COVID-19 disease in both control and patient groups (p=0.046).

Table 4: Allele frequency of rs34224237 of IL6 among COVID-19 patients and control

	Case NO: 50	Control: 50	OR	p. value
AAAAAAAA	41	28	1.9	0.046
AAAAAAAA+ AAAAAAAAA	33	44		

There was non-significantly relation (P. value= 0.03) between the expected genotype and the observed genotype for rs34224237, as shown in Table (5).

Table5:Hardy-Weinberg Equilibrium in of rs34224237 of lL 6among control.

Genotype of **rs34224237**	**AAAAA AAA**	**AAAAA AAAA**	**AAAAA AAAAA**	**p. value**
Observed genotype	6	32	12	0.03
Expected genotype	9.68	24.64	15.68	
HWE	(49.28%)	(32%)	(64%)	

According to the distribution of IL-6, rs34224237 SNP in this study population under the recessive and dominant model (Table 6 and 7) showed non-significantly results, so appeared the dominant model (AAAAAAAAA+ AAAAAAAAAA), (OR=1.7), more sensitive infected in COVID-19 than recessive model

Table 6: Distribution of rs34224237 of IL6 SNP in this study population under the recessive model

rs34224237	**Case NO:50**	**Control:50**	**OR**	**P. value**
AAAAAAAA+ AAAAAAAAA	40	38	1.26	0.6
AAAAAAAAAA	10	12		

Table 7: Distribution of rs34224237 of IL6 SNP in this study population under the dominant model.

rs34224237	**Case NO:25**	**Control: 25**	**OR**	**P. value**
AAAAAAAA	14	12	1.7	0.3
AAAAAAAAA+ AAAAAAAAAA	26	38		

There are three polymorphic patterns: AA, AG, and GG. The GG status was detected in the majority of samples in cases (42/50) and controls (26/50), while the AA pattern was observed in both cases (8/50) and controls (12/50). The AG pattern was detected only the control (12/50) of rs1800871 SNP, as in Table (8).

Table 8: Genotype frequency of rs1800871 A>G *IL10* among COVID 19 and control

rS1800871 A>G	Case=50	Control=50	OR	P. value
AA	8(%)	12 (%)	0.6	0.03
AG	0(%)	12 (%)	0.03	0.02
GG	42(%)	26 (%)	4..8	0.001

such allele frequency of IL-10, rs1800871 SNP among COVID-19 patients and control groups were noted.

Table 9 illustrates the statistically significant association (p. value 0.002) between the rs1800871 polymorphisms in the IL-10 gene and the development of COVID-19 disease.

Table 9: Allele frequency of rs1800871 T>C *IL10* among COVID-19 and the control.

RS1800871 A>G	**Case NO: 25**	**Control:25**	**OR**	**P. value**
A	16	36	0,3	0.002
G	84	64		

There were high significantly association (P. value: 0.0007) between expected genotype and observed genotype for rs1800871 SNP, as shown in Table (10).

Table (10) : Hardy-Weinberg equilibrium in of rs1800871 A>G *IL10* among the control group.

Genotype	AA	AG	GG
Observed genotype	12	12	26
Expected genotype	6.48	23.04	20.48
H-W Freq.	(12.96%)	(46.08%)	(40.96%)
Chi-squared 11.48 Df 1 p=0.0007			

Conferring to distribution of IL-10, rs1800871 SNP in current study population under recessive and dominant model (Table 11 and 12) shown a significantly results, so appeared the dominant model (AG+GG),(OR=0.6), more sensitive infected with COVID 19 than recessive model.

Table 11: Distribution of rs1800871 A>G IL10 SNP in this study population under recessive model

Genotype	**Case NO:50**	**Control:50**	**OR**	**P. value**
AA+AG	8	24	0.2	0.007
GG	42	26		

Table 12: Distribution of rs1800871 A>GIL10 SNP in this study population under the dominant model.

Genotype	**Case NO: 25**	**Control:25**	**OR**	**P. value**
AA	8	12	0.6	0.3
AG+GG	42	38		

IV. Discussion

The current results of distribution COVID-19 depending on age groups, appeared that the age group (52-70) years recorded the highest percentage (36%) who were infected with COVID-19, whereas the lowest percentage was shown in (22-31) years age group. When assessing the seriousness of COVID-19 individuals, age was a significant factor. Additionally, the host is harmed directly and indirectly by SARS-CoV-2, improving COVID-19 patient care [18]. A strong inflammatory response that includes a broad range of substances, including IL-6 and IL-10, indicates of the advancement of COVID-19.

These specific cytokines have different effects and are released in inflamed tissues with varying effects. In conditions of sepsis and significant organ damage, many cell types such as lymphocytes, macrophages, epithelial cells, endothelial cells, and fibroblasts, release them into circulation [19]. [20] suggested prognostic signs for COVID-19 patients that are quick to detect: IL-6 and IL-10 in 2021 after doing a thorough . It is possible that a genotype that results in poor IL-10 production could raise

the chance of having severe COVID-19 because of an inability to control inflammation, considering the significance of IL-10 in lowering inflammation. Given that this would contribute to developing severe disease, IL-10 would be a strong contender as a mediator in the gene-environment interaction. Therefore, a particular genetic variant may be a helpful prognostic marker if it is discovered to be linked to the severity of COVID-19 [21-23].

The current results for rs34224237 of IL-6 showed a non-significant result (P= 0.03). The examined samples (COVID 19 and control) contained the targeted high-frequency (AAAAAAAAA SNP). Numerous lung parenchyma cells, such as type II pneumocytes, T lymphocytes, and alveolar macrophages, generate IL-6. according to [22]. IL-6 is a pleiotropic cytokine that plays a significant role in controlling inflammatory and immune responses. Since IL-6 is an acute-phase inflammatory cytokine, monitoring circulating IL-6 could provide insight into the lungs' level of inflammation [24]. According to [25] IL-6 produced by inflammatory monocytes may cause severe lung inflammation and pulmonary function impairment in patients with severe COVID-19.

In an effort To discover a relationship between genetics and the immune system, single nucleotides have been connected to immunological responses. This process, known as "immunogenetic profiling," may lead to novel approaches to diagnosing and treating for certain diseases [26]. There was no discernible correlation between the severity of COVID-19 and IL-6-174G/C, according to [27]. Furthermore, [28] investigation did not discover any associations between the death rate and the patients with COVID-19 and their IL-6 gene polymorphisms [29]. findings indicated a correlation between the severity of COVID-19 and the IL6 gene polymorphism, particularly in the Caucasian population.

Moreover, [30] found that the immunogenetic influence of IL6 polymorphisms, as seen in viral and lung diseases may consider IL6 polymorphism as a major factor influencing the severity of COVID-19 and may help understand the COVID-19 therapy response. Death, ARDS, and cytokine storms are a few of the immunological reactions that the COVID-19 infection causes. IL-10 is a multifunctional cytokine that typically lowers inflammation or suppresses the immune system, but it can also have the opposite effect in human cancers and other autoimmune illnesses [30]; [31].Furthermore, the pneumonia patients found that there was a 2.42-fold increased risk of septic shock after pneumonia in those with interleukin(IL-6 –174G/C [32]. This suggests that those with the IL-6 –174C allele are more likely to get severe pneumonia because of their increased IL-6 production. This is supported by a study that found a strong correlation between the CC genotype and higher interleukin-6(IL-6) levels [32].In the current investigation, the rs34224237 SNP's allele frequency and genotype of IL-6 were shown to be significantly different between COVID-19 patients and controls (P=0.046); additionally, there was a significant relationship found to exist between the predicted and observed genotypes of rs34224237 (P value: 0.03).

In the Lithuanian population, The CC genotype of IL-6 rs1800795 SNPs and the AA genotype of IL-6 rs1800797 SNPs were shown to be significantly correlated, as well as several other genetic polymorphisms of IL-6, including rs1800796 and rs1800795 [34].The G allele of IL-6-174G/C was discovered to be more prevalent than the C allele in both the sick group (87%) and the control group (90%) by [27].However, [28]. investigation revealed that the G allele (68.6%) was the most often found allele.

The current results recorded a high significant result (P=0.0007) of the rs1800871 (A>G) SNP of the IL-10 gene and COVID. By suppressing the inflammatory response, IL-10 can potentially mitigate the damage caused by exaggerated immune reactions [35].

The results of this study documented a high significant relation between IL-10 with rs1800871 (A>G SNP) and the developing of COVID-19 disease in two groups of COVID-19 patients and healthy Iraqi people.

IL-10 gene, found on the locus 1q31-32, is very polymorphic. Several SNP and microsatellites have been identified throughout this gene. These polymorphisms alter the expression and function of the IL-10 molecule and thus influence the immune response. Single nucleotide polymorphisms in the promoter at positions -2849, -1082, -819, -592, -276, and -108, and ATA haplotype of three polymorphisms at -276, -147, and -108 have been found to affect IL-10 production [36], [33].Patients who get severely or critically unwell after contracting COVID-19 had higher concentrations of the inflammatory cytokine IL-10 [38] [37].As an anti-inflammatory cytokine, this cytokine was essential to the immunological response against COVID-19. It also assisted in immune system regulation avoiding of exaggerated inflammation [39].

Similarity, the allele frequency of IL-10, rs1800871 SNP among COVID 19 patients and control was statistically significant (p. value 0.002), and there was high significant association (P. value: 0.0007) between the expected and observed genotype for rs1800871 SNP.

The frequency of IL-10 polymorphisms in different populations; also, the allele and genotype frequencies of IL-10 polymorphisms vary considerably between populations. Studies of different populations show that some polymorphisms are rare in some ethnic groups but common in others. For example, the -627 and -572 polymorphisms are rarer in Caucasians than Asians. This variation in the frequency of polymorphisms between different populations may contribute to different disease susceptibilities and severity in these populations by altering their IL-10 immune response, [39,40].

It aids in maintaining the proper ratio of pro-to anti-inflammatory reactions, which is crucial for preventing the immunological dysregulation present in severe COVID-19 instances. Severe COVID-19 patients frequently have much lower levels of IL-10; this insufficient IL-10 production may be a factor in the severe cases' heightened inflammatory response [35], [42].

There are five exons and four introns in the IL-10 gene,and It can be found on chromosome 1 (1q31-q32).

Single-nucleotide polymorphisms are the most prevalent type of genetic variation (SNP). Several disorders have been thoroughly investigated in relation to three SNPs in the SNP database that are IL-10 promoters: rs1800896 (-1082A/G), rs1800871 (-819T/C), and rs1800872 (-592A/C) [43].

Data from a study of American Caucasians found that the -1082 G allele was significantly more frequent in healthy controls than in patients with severe sepsis, a disease associated with high IL-10 levels and profound immune suppression, suggesting that the allele is protective. This is supported by a lower frequency of the -1082 G allele in patients with aggressive periodontitis, a disease characterized by bone destruction in response to bacterial infection. Data on the -1082 A/G polymorphism from a study of Chinese, Malay, and Indian patients with tuberculosis and healthy controls was also consistent with a protective effect of the G allele, with lower frequency of the G allele in patients with more active disease, and a trend to an inverse dose effect between the number of G alleles and extent of disease. These studies require confirmation in larger data set , different populations, and functional studies to clarify allele-specific effects on IL-10 production and disease susceptibility [44].

V. CONCLUSIONS

The current results concluded that the polymorphism of IL-10 (rs1800871, A>G SNP) is associated with COVID-19 infection, and this polymorphism may be used as biomarkers to help identify those who are most likely to experience severe COVID-19.

CONFLICT OF INTEREST

Author declares that he has no conflict of interest.

REFERENCES

[1] C.-C. Lai, T.-P. Shih, W.-C. Ko, H.-J. Tang, and P.-R. Hsueh, "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges," *International Journal of Antimicrobial Agents*, vol. 55, no. 3, p. 105924, Feb. 2020.

[2] J. F.-W. Chan et al., "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster," *The Lancet*, vol. 395, no. 10223, Jan. 2020.

[3] Y. Jamilloux et al., "Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions," *Autoimmunity Reviews*, vol. 19, no. 7, p. 102567, Jul. 2020.

[4] R. de C. C. M. de Brito, N. Lucena-Silva, L. C. Torres, C. F. Luna, J. de B. Correia, and G. A. P. da Silva, "The balance between the serum levels of IL-6 and IL-10 cytokines discriminates mild and severe acute pneumonia," *BMC Pulmonary Medicine*, vol. 16, no. 1, Dec. 2016.

[5] S. Roy and P. Ghosh, "Factors affecting COVID-19 infected and death rates inform lockdown-related policymaking," *PLOS ONE*, vol. 15, no. 10, p. e0241165.

[6] I. Jančić et al., "-174G/C interleukin-6 gene promoter polymorphism predicts therapeutic response to etanercept in rheumatoid arthritis," *Rheumatology International*, vol. 33, no. 6, pp. 1481–1486, Dec. 2012.

[7] M. K. Vakil et al., "Individual genetic variability mainly of Proinflammatory cytokines, cytokine receptors, and toll-like receptors dictates pathophysiology of COVID-19 disease," *Journal of Medical Virology*, vol. 94, no. 9, pp. 4088–4096, May 2022.

[8] K. W. Moore, R. de Waal Malefyt, R. L. Coffman, and A.O'Garra," Interleukin-10 and the interleukin-10 Receptors," *Annual Review of Immunology*, vol. 19, no. 1,pp. 683–765, Apr. 2001.

[9] H. Li et al., "SARS-CoV-2 and viral sepsis: observations and hypotheses," *The Lancet*, vol. 395, no. 10235, Apr. 2020.

[10] D. Fiorentino, A. Zlotnik, T. R. Mosmann, M. A. Howard, and A. O'Garra, "IL-10 inhibits cytokine production by activated macrophages.," *Clinical Rheumatology* vol. 147, no. 11, pp. 3815–3822, Dec. 1991.

[11] O. Ates, G. Hatemi, V. Hamuryudan, and A. Topal-Sarikaya, "Tumor necrosis factor-alpha and Interleukin-10 gene promoter polymorphisms in Turkish rheumatoid arthritis patients," *Clinical Rheumatology*, vol. 27, no. 10, pp. 1243–1248, Apr. 2008.

[12] C. Huang et al., "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China," *The Lancet*, vol. 395, no. 10223, pp. 497–506, Jan. 2020.

[13] C. R. Triggle et al., "A Comprehensive Review of Viral Characteristics, Transmission, Pathophysiology, Immune Response, and Management of SARS-CoV-2 and COVID-19 as a Basis for Controlling the Pandemic," *Frontiers in Immunology*, vol. 12, Feb. 2021.

[14] S. Wang et al., "Cytokine Storm in Domestic Pigs Induced by Infection of Virulent African Swine Fever Virus," *Frontiers in Veterinary Science*, vol. 7, Jan. 2021.

[15] W. Yang et al., "Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China," *Journal of Infection*, vol. 80, no. 4, Feb. 2020.

[16] X. Yang et al., "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study," *The Lancet Respiratory Medicine*, vol. 8, no. 5, pp. 475–481, Feb. 2020.

[17] D. Wang et al., "Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China," *JAMA*, vol. 323, no. 11, pp. 1061–1069, Feb. 2020.

[18] S. Najmeh, J. Marzieh, L. Arash, K. Shahzamani, S. Dashti, and T. Gholamreza, "Association of IL-10 Gene in Protection Against COVID-19 Disease," Jundishapur *Journal of Microbiology*, vol. 16, no. 7, Aug. 2023.

[19] S. Preciado, S. Muntión, and Fermín Sánchez-Guijo, "Improving hematopoietic engraftment: Potential role

of mesenchymal stromal cell-derived extracellular vesicles," *Stem Cells*, vol. 39, no. 1, pp. 26–32, Oct. 2020.

[20] S. K. Dhar, V. K, S. Damodar, S. Gujar, and M. Das, "IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression," *Heliyon*, vol. 7, no. 2, p. e06155, Feb. 2021.

[21] E. Sattar, and F. Abolfazl, "Association between interleukin-10 gene polymorphisms (rs1800871, rs1800872, and rs1800896) and severity of infection in different SARS-CoV-2 variants," *Human genomics* (Print), vol. 17, no. 1, Mar. 2023.

[22] S. Rizvi et al., "Implication of single nucleotide polymorphisms in Interleukin-10 gene (rs1800896 and rs1800872) with severity of COVID-19," *Egyptian Journal of Medical Human Genetics*, vol. 23, no. 1, Oct. 2022.

[23] Z. Degaim et al., "Detection of intracellular adhesion (ica) B gene in Staphylococcus aureus isolated from wound infections," *University of Thi-Qar Journal of Medicine*, Apr. 2019.

[24] R. de C. C. M. de Brito, N. Lucena-Silva, L. C. Torres, C. F. Luna, J. de B. Correia, and G. A. P. da Silva, "The balance between the serum levels of IL-6 and IL-10 cytokines discriminates mild and severe acute pneumonia," BMC Pulmonary *Medicine*, vol. 16, no. 1, Dec. 2016.

[25] Y. Zhou et al., "Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus, *National Science Review* Volume 7, Issue 6 Pp. 998–1002" Feb. 2020.

[26] N. Kirtipal and S. Bharadwaj, "Interleukin 6 polymorphisms as an indicator of COVID-19 severity in humans," *Journal of Biomolecular Structure and Dynamics*, vol. 39, no. 12, pp. 4563–4565, Jun. 2020.

[27]S. Aladawy, L. Adel, S. Abdel Salam, R. Raafat, and M. Khattab, "Polymorphism in promotor region of IL6 gene as a predictor for severity in COVID -19 patients," *Egyptian journal of Immunology*, vol. 29, no. 2, pp. 01–09, Apr. 2022.

[28] L. Karcioglu Batur and N. Hekim, "The role of DBP gene polymorphisms in the prevalence of new coronavirus disease 2019 infection and mortality rate," *Journal of Medical Virology*, vol. 93, no. 3, pp. 1409–1413, Aug. 2020.

[29] Z. S. Ulhaq and G. V. Soraya, "Anti-IL-6 Receptor Antibody Treatment for Severe COVID-19 and the Potential Implication of IL-6 Gene Polymorphisms in Novel Coronavirus Pneumonia," *SSRN Electronic Journal*, 2020.

[30] A. Naing et al., "Safety, Antitumor Activity, and Immune Activation of Pegylated Recombinant Human Interleukin-10 (AM0010) in Patients With Advanced Solid Tumors," *Journal of Clinical Oncology*: *Official Journal of the American Society of Clinical Oncology*, vol. 34, no. 29, pp. 3562–3569, Oct. 2016.

[31] Z. Degaim et al., "Detection of clfA Gene in Staphylococcus aureus Isolated From Tonsillitis Patients," *College of Education for Pure Science Journal*, vol. 9, no. 1, pp.184189,Mar.2019.

[32] Z.-R. Mao, S.-L. Zhang, and B. Feng, "Association of IL-10 (-819T/C, -592A/C and -1082A/G) and IL-6 -174G/C gene polymorphism and the risk of pneumonia-induced sepsis," *Biomarkers*, vol. 22, no. 2, pp. 106–112, Aug. 2016.

[33] N. Vadgama et al., "SARS-CoV-2 Susceptibility and ACE2 Gene Variations Within Diverse Ethnic Backgrounds," *Frontiers in Genetics*, vol. 13, Apr. 2022.

[34] A. Vitkauskaite et al., "IL-6 597A/G (rs1800797) and 174G/C (rs1800795) Gene Polymorphisms in the Development of Cervical Cancer in Lithuanian Women," *Medicina*, vol. 57, no. 10, p. 1025, Sep. 2021.

[35] H. Han et al., "Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors," *Emerging Microbes & Infections*, vol. 9, no. 1, pp. 1123–1130, Jan. 2020.

[36] M. Palivonaite, G. Gedvilaite, B. Glebauskiene, L. Kriauciuniene, V. Rovite, and R. Liutkeviciene, "IL-10 Gene Rs1800871, Rs1800872, and Rs1800896 Polymorphisms and IL-10 Serum Levels Association with Pituitary Adenoma," *Biomedicines*, vol. 10, no. 8, p. 1921, Aug. 2022.

[37] T. Men *et al.*, "The impact of interleukin-10 (IL-10) gene 4 polymorphisms on peripheral blood IL-10 variation and prostate cancer risk based on published studies," *Oncotarget*, vol. 8, no. 28, pp. 45994–46005, Apr. 2017.

[38] B. Diao et al., "Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19)," *Frontiers in Immunology*, vol. 11, May 2020.

[39] E. Benetti et al., "ACE2 gene variants may underlie inter individual variability and susceptibility to COVID-19 in the Italian population," *European Journal of Human Genetics*, vol. 28, no. 11, pp. 1602–1614, Jul. 2020.

[40] Santos, R. Luiz, J. L. Paz, Maria, K. Valéria, and L. Nepomuceno, "Study of TNF-α, IFN-γ, TGF-β, IL-6, and IL-10 gene polymorphism in individuals from the leprosy endemic area in the Brazilian Amazon*," Meta Gene*, vol. 25, pp. 100740–100740, May 2020.

[41] M. Jasim, A. Mater, and D. Zainab Dakhil, "Detection of intracellular adhesion (ica) B gene in Staphylococcus aureus isolated from wound infections," *University of Thi-Qar Journal Of Medicine*, vol. 16, no. 2, pp. 185–192, 2018, Accessed: Dec. 05, 2024.

[42] M. Braga et al., "Influence of IL10 (rs1800896) Polymorphism and TNF-α, IL-10, IL-17A, and IL-17F Serum Levels in Ankylosing Spondylitis," *Frontiers in Immunology*, vol. 12, Jul. 2021.

[43] D. J. Langton et al., "The influence of HLA genotype on the severity of COVID-19 infection*," HLA*, vol. 98, no. 1, pp. 14–22, May 2021.