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Coronavirus Pandemic

Influence of IL-6 rs1800795 and IL-8 rs2227306 polymorphisms on COVID-19 outcome

Amany A Ghazy[1]

[1] Department of Pathology, Microbiology and Immunology Division, College of Medicine, Jouf University, Sakaka, Saudi Arabia

Abstract

Introduction: Severe coronavirus disease 2019 (COVID-19) is mainly precipitated by an uncontrolled inflammatory response and cytokine storm. Pro-inflammatory cytokines such as IL-6 and IL-8 levels were markedly increased in complicated cases. Genetic polymorphisms may have a role in this dysregulated expression during SARS-CoV-2 infection. Our aim was to assess the influence of IL-6 and IL-8 single nucleotide polymorphisms (SNPs) on COVID-19 outcomes.

Methodology: 240 subjects were involved in the study; 80 cases with severe COVID-19, 80 cases with mild COVID-19, and 80 healthy subjects. IL-6rs1800795(G/C) and IL-8 rs2227306(C/T) genotyping was performed using real-time polymerase chain reaction (PCR).

Results: Ages ranged between 20-67 years in all groups. There was a statistically significant association between the male gender and severe COVID-19. A significantly higher expression of IL-6rs1800795GG and IL-8rs2227306CC genotypes was observed among patients with severe COVID-19 than other groups. At the allele level, IL-6rs1800795G and IL-8rs2227306C alleles were more frequent among patients with severe COVID-19 when compared with other groups. Haplotypes' frequency clarified that the coexistence of IL-6 rs1800795G and IL-8rs2227306C alleles in the same person increased the risk of severe COVID-19 outcomes. Carriers of IL-6rs1800795C and IL-8 rs2227306T alleles are at lower risk of developing severe COVID-19. Multivariate logistic regression analysis showed that old age, male gender, IL-6 rs1800795CG+GG, and IL-8 rs2227306CT+CC genotypes could be independent risk factors for severe COVID-19 outcomes.

Conclusions: IL-6 rs1800795G and IL-8 rs2227306C alleles are significantly associated with severe COVID-19 outcomes, especially if they coexist. They may be used as prognostic markers for COVID-19.

Key words: IL-6 rs1800795; IL-8 rs2227306; SNP; COVID-19; outcome.

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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that causes vascular endothelium injury, activation of the coagulation cascade, thrombosis, pneumonia, and shortness of breath [1]. It was noticed that patients with severe and complicated forms of COVID-19 have a dysregulated hyper-inflammatory immune response, known as cytokine release syndrome (CRS), precipitated by SARS-CoV-2 [2-5]. They had very high levels of Interleukin (IL)-6 levels (> 200 mg/L) and IL-8 (1500 pg/mL) when compared with uncomplicated cases. Thus, IL-6 and IL-8 are suggested to have a significant role in CRS, multi-organ dysfunction, respiratory failure, and shock [1-3,6].

Interleukin (IL)-6 is a pleiotropic inflammatory cytokine secreted from many cells (including fibroblasts, endothelial cells, monocytes, mast cells, macrophages, and dendritic cells) in response to tissue damage and/or infections. IL-6 has multiple roles such as induction of C-reactive protein (CRP) release, increasing T helper (Th)-2 and Th17 cell responses, control of monocytes' differentiation to macrophages, inflammation, activation of B-cells and immunoglobulin G (IgG) production, and inducing the cytolytic capacity of cytotoxic T-lymphocytes (CTL) [7].

IL-8 has a role in inflammation, recruitment of immune cells, neutrophil activation, and degranulation [8]. In SARS-CoV-2 infection, it was reported that the prothrombotic, degranulated neutrophil phenotype in severe COVID-19 is associated with increased IL-8 release and expression on neutrophils recruited to the pulmonary tissue which, in turn, activates IL-8 production from peripheral neutrophils as sustained loops [6].

Genetic mutations such as single nucleotide polymorphisms (SNP) could influence the molecular mechanisms and pathogenesis of any disease with

variable outcomes in different populations [8]. Recently, we have studied the role of IL-6 and IL-8 SNPs in prostate cancer and found a significant association between IL-6 rs1800795 G and IL-8 rs2227306 C alleles and cancer development, particularly when they coexist [8].

Genetic polymorphisms in IL-6 and/or IL-8 genes in SARS-CoV-2 infected patients may significantly affect their dysregulated production and expression. Thus this research aims to assess the influence of IL-6 and IL-8 gene polymorphisms on COVID-19 outcomes that may provide a reliable screening tool to predict the outcome of COVID-19.

Methodology

Study Design

The study enrolled 240 persons; 80 patients with severe COVID-19, 80 patients with mild COVID-19 symptoms, and 80 who were age- and gender-matched healthy individuals. Inclusion criteria for COVID-19 were positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2, high temperature, headache, cough, and fatigue. The severity of COVID-19 was adjudicated as follows: (1) mild COVID-19 patients have mild clinical symptoms, O_2 saturation > 93%, and no pneumonia on lung computed tomography (CT); (2) severe COVID-19 patients have O_2 saturation ≤ 93% at rest, respiratory rate > 30/minute, severe pneumonia on lung CT, and severe clinical manifestations [9,10]. Exclusion criteria were cardiac, hepatic, renal decompensation, and autoimmune diseases. Vaccination status and comorbidities such as hypertension, diabetes mellitus, and hepatic fibrosis were determined during history taking.

Ethics approval

The study protocol has been revised and approved by the Ethics Review Committee of the Faculty of Medicine, Kafrelskeikh University, Egypt, on 7th September 2020. The study followed the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was collected from participants.

Samples

Four mL of venous blood was drawn from all the subjects for DNA extraction and genotyping.

IL-6 rs1800795 and IL-8 rs2227306 genotyping

Genomic DNA was extracted from the blood samples using QIAamp DNA Blood Mini Kit (Applied Biosystems, ThermoFisher Scientific, Foster City, USA). IL-6 rs1800795 (G/C) and IL-8 rs2227306 (C/T) SNPs genotyping was performed using TaqMan dual-labeled probes, as described by Ghazy *et al*. (2021) [8]. Genotypes were determined by the increased fluorescence signal when the probes hybridized to the complementary sequence in the tested samples and were cleaved from the dye. A significant increase in VIC dye only indicated homozygous for the 1st allele, in FAM dye indicated homozygous for the 2nd allele, and if both signals increased, this specified heterozygous genotypes [9]. In each run, samples without DNA were used as negative controls and three random samples were repeated to ensure reproducibility.

Statistical analysis of the data

The data were analyzed using the IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Kolmogorov- Smirnov test was performed to verify the normal distribution of variables. The equilibrium of the studied samples was tested by the Hardy-Weinberg equation (HWE). Qualitative data were expressed as numbers and percentages. Comparisons between groups were performed using the Chi square, and Monte Carlo tests. Odds ratios (OR) with 95% confidence intervals (CI) were used to

Table 1. Comparison between the studied groups according to demographic and clinical data.

Demographic and clinical data	Negative control (N = 80)	Mild COVID-19 (N = 80)	Severe COVID-19 (N = 80)	*p* value
Age (years)				
Median (Min – Max)	45 (22 – 65)	41 (27 – 67)	49 (21 – 64)	0.055
Gender				
Men	27 (33.8%)	27 (33.8%)	46 (57.5%)	0.002*
Women	53 (66.3%)	53 (66.3%)	34 (42.5%)	
Vaccination status				
Vaccinated	80 (100%)	73 (91.3%)	41 (51.3%)	< 0.001*
Comorbidities				
Hypertension	0 (0%)	11 (13.75%)	14 (17.5%)	
Diabetes mellitus	0 (0%)	5 (6.25%)	23 (28.75%)	0.003
Hepatic fibrosis	0 (0%)	0 (0%)	8 (10%)	

* Statistically significant at $p \leq 0.05$.

Table 2. Hardy-Weinberg for different SNPs in each group.

	Control (n = 80)	Mild COVID-19 (n = 80)	Severe COVID-19 (n = 80)
IL-6 rs1800795			
CC^R	48 (60%)	42 (52.5%)	21 (26.3%)
CG	25 (31.3%)	34 (42.5%)	39 (48.8%)
GG	7 (8.8%)	4 (5%)	20 (25%)
^{HW}p	$p = 0.173$	$p = 0.382$	$p = 0.824$
IL-8 rs2227306			
TT^R	44 (55%)	44 (55%)	14 (17.5%)
CT	32 (40%)	32 (40%)	29 (36.3%)
CC	4 (5%)	4 (5%)	37 (46.3%)
^{HW}p	$p = 0.551$	$p = 0.551$	$p = 0.061$

HW: Hardy-Weinberg equilibrium; R: Reference group; *p*: *p* value for Chi square goodness of fit; *: Statistically significant at $p \leq 0.05$.

calculate the risk of an event in the studied groups. Statistical significance was set at 5%.

Results

Subjects' demographic data

The age of the subjects ranged between 21–64, 27–67, and 20–65 years in the severe COVID-19, mild COVID-19, and negative control groups, respectively. No statistically significant difference in age was found among the studied groups *(p* = 0.055). Gender distribution, vaccination history, and history of comorbidities of the participants are presented in Table 1. There was a statistically significant association between severe COVID-19 and the male gender ($p = 0.002$). Vaccination history showed that all controls had received the COVID-19 vaccine while 48.8% and 8.8% of severe and mild COVID-19 cases were not vaccinated against this infection ($p < 0.001$) (Table 1). Furthermore, nearly half of patients with severe COVID-19 had comorbidities such as hypertension, diabetes mellitus, and hepatic fibrosis ($p = 0.003$).

IL-6 rs1800795 (G/C) genotypic and allelic distribution

Differences between the observed and expected frequencies of genotypes and alleles among the studied groups were tested using the HWE. No statistically significant differences were found between the studied groups (Table 2).

Genotyping of IL-6 rs1800795 (G/C) showed the expression of all genotypes in all groups. However, the frequency of IL-6 rs1800795CC genotype was higher among mild COVID-19 patients (52.5%) and negative controls (60%) than among severe COVID-19 patients (26.3%). However, there was a marked increase in IL-6 rs1800795 GG genotype frequency among patients with severe COVID-19 (25%) compared with the other groups (5% among mild COVID-19 ($p < 0.001$), and 8.8% among the negative controls ($p < 0.001$)). At the allele level, the frequency of IL-6 rs1800795 G allele was higher among patients with severe COVID-19 (49.4%) than mild cases (26.3%) ($p < 0.001$) and negative controls (24.4%) ($p < 0.001$). IL-6 rs1800795 C allele frequency was higher among mild cases (73.8%) and negative controls (75.6%) than among severe COVID-19 patients (50.6%) ($p < 0.001$) (Table 3).

Table 3. Comparison between the three studied groups according to different SNPs.

SNPs	Control (n = 80)	Mild COVID-19 (n = 80)	Severe COVID-19 (n = 80)	Significance between groups
IL-6 rs1800795				
CC^R	48 (60%)	42 (52.5%)	21 (26.3%)	$p_1 = 0.274$,
CG	25 (31.3%)	34 (42.5%)	39 (48.8%)	$p_2 < 0.001^*$,
GG	7 (8.8%)	4 (5%)	20 (25%)	$p_3 < 0.001^*$
Allele				$p_1 = 0.700$,
C^R	121 (75.6%)	118 (73.8%)	81 (50.6%)	$p_2 < 0.001^*$,
G	39 (24.4%)	42 (26.3%)	79 (49.4%)	$p_3 < 0.001^*$
IL-8 rs2227306				
TT^R	44 (55%)	44 (55%)	14 (17.5%)	$^{MC}p_1 = 1.000$,
CT	32 (40%)	32 (40%)	29 (36.3%)	$p_2 < 0.001^*$,
CC	4 (5%)	4 (5%)	37 (46.3%)	$p_3 < 0.001^*$
Allele				$p_1 = 1.000$,
T^R	120 (75%)	120 (75%)	57 (35.6%)	$p_2 < 0.001^*$,
C	40 (25%)	40 (25%)	103 (64.4%)	$p_3 < 0.001^*$

MC: Monte Carlo, p_1: *p* value for Chi square test for comparing between control and mild COVID-19, p_2: *p* value for Chi square test for comparing between control and severe COVID-19, p_3: *p* value for Chi square test for comparing between mild and severe COVID-19, *: Statistically significant at $p \leq 0.05$

Table 4. Univariate analysis for severe COVID-19 cases regarding to different SNPs.

SNPs genotypes & alleles	Severe vs. Mild[R]		Severe vs. Control[R]	
	p	OR (LL – UL 95%CI)	*p*	OR (LL – UL 95% CI)
IL-6 rs1800795				
CC[R]		1.000		1.000
CG	0.020*	2.294 (1.143 – 4.606)	0.001*	3.566 (1.740 – 7.309)
GG	< 0.001*	10.000 (3.029 – 33.019)	< 0.001*	6.531 (2.398 – 17.786)
Allele				
C[R]		1.000		1.000
G	< 0.001*	2.740 (1.714 – 4.380)	< 0.001*	3.026 (1.880 – 4.869)
IL-8 rs2227306				
TT[R]		1.000		1.000
CT	0.009*	2.848 (1.301 – 6.236)	0.009*	2.848 (1.301 – 6.236)
CC	< 0.001*	29.071 (8.808 – 95.953)	< 0.001*	29.071 (8.808 – 95.953)
Allele				
T[R]		1.000		1.000
C	< 0.001*	5.421 (3.346 – 8.782)	< 0.001*	5.421 (3.346 – 8.782)

OR: Odd's ratio; [R]: Reference group; CI: Confidence interval; LL: Lower limit; UL: Upper Limit; *p*: *p* value for univariate regression analysis for comparing with the reference genotype; *: Statistically significant at $p \leq 0.05$.

Table 5. Haplotype frequency for IL-6 and IL-8 in the three study groups.

IL-6 and IL-8	Haplotype frequencies (%)			Severe vs. Mild COVID-19®		Severe COVID-19 vs. Control®	
	Control (n = 160)	Mild (n = 160)	Severe (n = 160)	p_1	OR (95%CI) (LL – UL)	p_2	OR (95% CI) (LL – UL)
CT[R]	85 (53.1%)	80 (50%)	24 (15%)		1.000		1.000
CC	36 (22.5%)	38 (23.8%)	57 (35.6%)	< 0.001*	5.000 (2.7 – 9.3)	< 0.001*	5.608 (3 – 10.4)
GT	35 (21.9%)	40 (25%)	33 (20.6%)	0.002*	2.750 (1.4 – 5.3)	< 0.001*	3.339 (1.7 – 6.4)
GC	4 (2.5%)	2 (1.3%)	46 (28.8%)	< 0.001*	76.667 (17.3 – 339.3)	< 0.001*	40.729 (13.3 – 124.5)

[R]: reference group; OR: odds ratio; CI: confidence interval; LL: lower limit; UL: upper limit; p_1: *p* value for comparing between severe and mild COVID-19; p_2: *p* value for comparing between severe COVID-19 and control; *: statistically significant at $p \leq 0.05$.

Table 6. Univariate and multivariate logistic regression analysis for the parameters affecting severe and mild COVID-19 (n = 80 vs 80).

	Univariate		[#]Multivariate	
	p	OR (LL – UL 95% CI)	*p*	OR (LL – UL 95% CI)
Age (/10 years)	0.020*	1.446 (1.061 – 1.971)	0.033*	1.487 (1.033 – 2.141)
Male	0.003*	2.656 (1.399 – 5.043)	0.007*	2.922 (1.349 – 6.329)
Not vaccinated	< 0.001*	9.920 (4.070 – 24.176)	< 0.001*	12.138 (4.470 – 32.963)
IL-6 rs1800795				
CG + GG	0.001*	3.105 (1.599 – 6.031)	0.003*	3.421 (1.520 – 7.698)

OR: Odd`s ratio; CI: confidence interval; LL: lower limit; UL: upper limit; #: All variables with $p < 0.05$ was included in the multivariate; *: Statistically significant at $p \leq 0.05$.

Table 7. Univariate and multivariate logistic regression analysis for the parameters affecting severe and mild COVID-19 (n = 80 vs. 80).

	Univariate		[#]Multivariate	
	p	OR (LL – UL 95%C.I)	*p*	OR (LL – UL 95% CI)
Age (/10 years)	0.020*	1.446 (1.061 – 1.971)	0.013*	1.622 (1.108 – 2.374)
Male	0.003*	2.656 (1.399 – 5.043)	0.002*	3.661 (1.598 – 8.388)
Not vaccinated	< 0.001*	9.920 (4.070 – 24.176)	< 0.001*	12.198 (4.257 – 34.949)
IL-8 rs2227306				
CT + CC	< 0.001*	5.762 (2.789 – 11.905)	< 0.001*	7.156 (2.951 – 17.355)

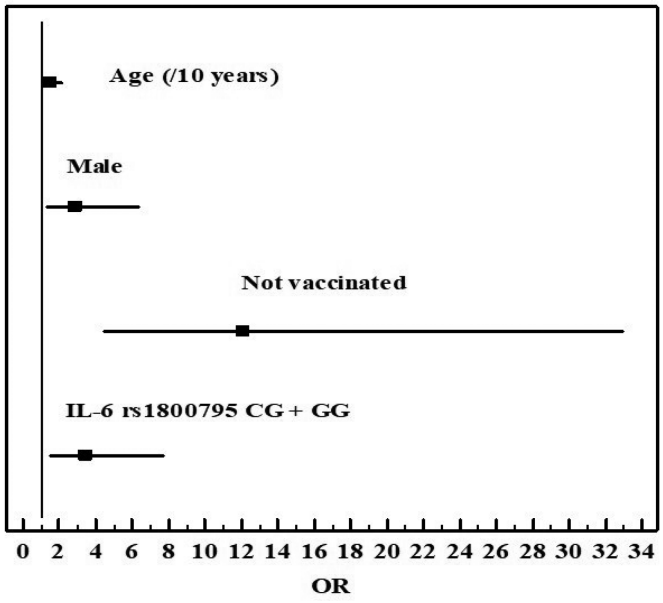
OR: Odd`s ratio; CI: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with $p < 0.05$ were included in the multivariate; *: Statistically significant at $p \leq 0.05$.

Univariate analysis of the studied alleles resulted in OR (95% CI) of 2.740 (1.714–4.380) when the G allele was compared between severe and mild COVID-19 patients and 3.026 (1.880 – 4.869) when severe COVID-19 patients were compared with the controls (Table 4).

IL-8 rs2227306 (C/T) genotypic and allelic distribution

Genotypic distribution of IL-8 rs2227306 (C/T) showed the presence of all genotypes in the three groups with marked disparities as IL-8 rs2227306 TT genotype frequency was higher among mild COVID-19 patients (55%) and negative controls (55%) than severe COVID-19 patients (17.5%). However, the IL-8 rs2227306CC genotype was expressed in few mild COVID-19 patients (5%) and negative controls (5%) in comparison with severe COVID-19 patients (46.3%). There was a statistically significant association between CC genotype and severe COVID-19 ($p < 0.001$). At the allele level, the frequency of IL-8 rs2227306 C allele was higher among patients with severe COVID-19 (64.4%) than among mild cases (25%) ($p < 0.001$) and negative controls (25%) ($p < 0.001$). While IL-8 rs2227306 T allele frequency was higher among mild cases (75%) ($p < 0.001$) and negative controls (75%) than severe COVID-19 patients (35.6%) ($p < 0.001$) (Table 3). Univariate analysis of the studied alleles resulted in an OR (95% CI) of 5.421 (3.346 – 8.782) with the C allele when comparing severe COVID-19 patients and the other groups (Table 4).

Figure 1. Multivariate logistic regression analysis for the parameters affecting severe and mild COVID-19 in relation to IL-6 (n = 80 vs. 80).



Study of haplotypes' frequency

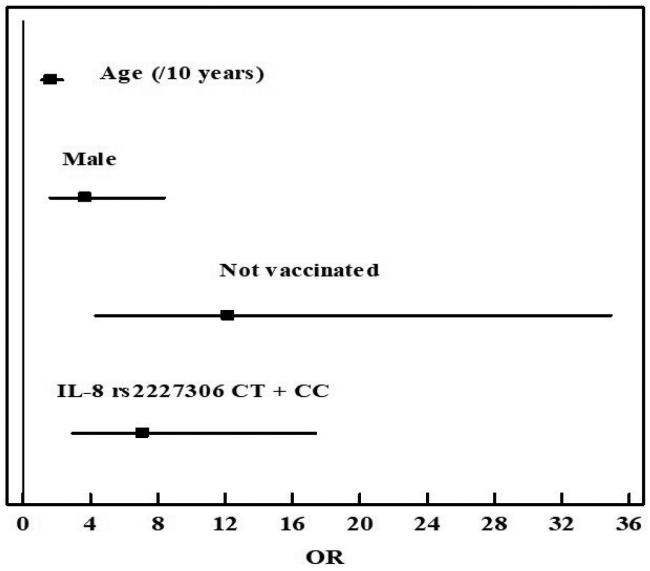
The study of haplotypes' frequency clarified that the coexistence of IL-6 rs1800795 G and IL-8 rs2227306 C alleles in the same person increased the risk of severe COVID-19 outcome. On the other hand, carriers of IL-6rs1800795C and IL-8 rs2227306T alleles are at lower risk of severe COVID-19 (Table 5). Multivariate logistic regression analysis for the studied parameters affecting COVID-19 showed that old age, male gender, non-vaccination, IL-6 rs1800795 CG + GG, and IL-8 rs2227306 CT + CC genotypes could be independent risk factors for severe COVID-19 outcome (Tables 6 and 7, Figures 1 and 2).

Discussion

The COVID-19 pandemic has disrupted the global economy and strained everyday human lives and healthcare systems. It was found that the key factor in COVID-19 pathology is the CRS, with massive production of many cytokines such as IL-6, IL-8, and tumor necrosis factor [11]. Since the discovery of IL-6 in 1973, it has been identified to have a pivotal role in immune regulation in health and dysregulation in many diseases including, COVID-19 [12].

Polymorphisms in IL-6 and/or IL-8 genes may account for the variability of their expression and disparities in the pathogenesis of various infectious diseases [8,13-15]. Recently, IL-6 rs1800795G and IL-8rs 2227306C alleles were reported to be risk factors for

Figure 2. Multivariate logistic regression analysis for the parameters affecting severe and mild COVID-19 in relation to IL-8 (n = 80 vs. 80).



prostate cancer [8]. Zhang *et al*. (2017) observed that IL-6 572 (rs1800795) C allele frequency is insignificantly higher among females with gestational diabetes mellitus [14]. However, the contribution of IL-6/8 SNP on COVID-19 clinical outcomes has not been thoroughly studied. Thus, the current study assessed the influence of IL-6 and IL-8 gene polymorphisms on COVID-19 outcomes aiming to shed light on a new reliable screening tool to predict the prognosis of this disease.

In this study, the ages ranged between 20 and 67 years in the studied groups without any statistically significant difference among them. However, males represented 57.5%, 33.8%, and 33.8% among severe COVID-19, mild COVID-19, and negative control groups, respectively. There was a statistically significant association between severe COVID-19 and the male gender ($p = 0.002$). This is in agreement with Nguyen *et al.* (2021) [16] and Chaturvedi *et al*. (2022) [17], who stated that males are at a higher risk for infectivity, and worse outcomes when compared with females. They suggested that genetic predispositions and sex hormones may affect the immune response and contribute to this disparity in COVID-19 outcomes [17].

Vaccination history showed that 48.8% of cases with severe COVID-19 were not vaccinated, while all controls and 91.2% of mild COVID-19 cases had received the vaccine against SARS-CoV2. The findings agree with Wright *et al*. (2022) [18], who found that vaccination against COVID-19 is highly effective against the development of severe COVID-19.

Genotyping of IL-6 rs1800795 (G/C) demonstrated that there was higher frequency of IL-6 rs1800795 G allele among patients with severe COVID-19 (49.4%) than mild cases (26.3%) and negative controls (24.4%) ($p < 0.001$) with higher OR (95% CI) in comparison with the other allele. This could be explained by the fact that IL-6 rs1800795 SNP affects the serum levels of IL-6, the main cytokine in the cytokine storm, which in turn augments the patient's immune system, and exacerbates the inflammatory responses resulting in deterioration of COVID-19 manifestations [13,19]. Thus IL-6 overproduction is considered a hallmark of severe COVID-19. This has been confirmed by Abobaker *et al.,* (2021) who have reported that IL-6 174G/C (rs1800795) polymorphism is associated with increased secretion of IL-6, high risk of severe pneumonia, and severe COVID-19 outcome [20]. Another study has confirmed that IL-6 rs1800795 polymorphism is a G to C transition mutation in the -174 position of the IL-6 gene promoter region which in turn affects the production of IL-6 [21].

Other researchers have found a significant association between IL-6 rs1800795 SNP and primary iron overload [22], cancer metastasis [21,23], non-small cell lung cancer [21], and ischemic stroke [24].

On the other hand, Chen *et al*. (2021) have found other IL-6 polymorphisms that decrease its transcription and secretion markedly such as IL-6rs1800797, rs1800795, and rs1800796 [13]. They reported that the C-T-T variant haplotype of these SNPs is associated with low serum levels of IL-6, and mild COVID-19 outcomes in Asian patients. They suggested that these polymorphisms disturb the stimulus-dependent transcription of IL-6, resulting in decreased IL-6 expression and attenuation of IL-6 response to viral infection.

Genotypic distribution of IL-8 rs2227306 (C/T) revealed that IL-8rs2227306 C allele was more frequent among patients with severe COVID-19 (64.4%) than in mild cases (25%) and negative controls (25%) ($p < 0.001$) with an OR (95% CI) of 5.421 (3.346–8.782). This SNP may also be associated with increased secretion of IL-8 that activates the prothrombotic neutrophil phenotype. These neutrophils initiate the coagulation and complement cascade, resulting in the immuno-thrombotic state of severe COVID-19 [6].

Kaiser *et al*. (2021) have identified higher IL-8 plasma levels among patients with severe COVID-19 than those with mild-to-moderate disease [6]. There were positive correlations between high IL-8 levels and severe pneumonia, high D-dimer plasma levels, dysregulated coagulation, and elevated neutrophil protein. They reported that blocking IL-8 results in the attenuation of neutrophil extracellular trapping, degranulation, and activation.

We noticed that coexistence of IL-6 rs1800795 G and IL-8 rs2227306 C alleles is associated with higher risk of severe COVID-19 outcomes. However, IL-6rs1800795C and IL-8 rs2227306T alleles are presented in cases with mild COVID-19 outcomes. Multivariate logistic regression analysis showed that old age, male gender, non-vaccination, IL-6 rs1800795 CG + GG, and IL-8 rs2227306 CT + CC genotypes could be independent risk factors for severe COVID-19 outcome.

This research provides further evidence that at the molecular level IL-6 rs1800795 G and IL-8rs2227306 C alleles are significantly linked to severe COVID-19 outcomes, particularly if they coexist. Both polymorphisms could affect the serum levels of IL-6 and IL8 and in turn the cytokine storm which is indicted

in the occurrence of severe COVID-19. Thus, they could be used as screening tools for high-risk groups such as older patients, pregnant females, and patients with chronic diseases. However, the main limitations of the current study are the small sample size, lack of comparison with serum levels of IL-6 and IL-8, and follow-up of patients to determine the mortality. Thus further research on a larger scale, including more comparative parameters, is recommended.

Conclusions

The presence of IL-6 rs1800795G and IL-8 rs2227306C alleles is significantly associated with severe COVID-19 outcome. Their existence heightens the risk of severe COVID-19 outcomes, especially if presented together. They could be used as prognostic markers for the severity of COVID-19 manifestations.

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Corresponding author

Amany A. Ghazy
Associate Professor of Microbiology & Immunology,
College of Medicine, Jouf University, Sakaka, Saudi Arabia
Tel: 00966146545394
Email: aaelshenawy@ju.edu.sa

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