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Association between IL-6 rs1800795 and IL-1β rs 16944 gene polymorphisms with clinical severity of COVID-19 patients in Surakarta, Central Java, Indonesia

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ABSTRACT

Background: Cytokine plays a pivotal role in the pathogenesis of coronavirus disease 2019 (COVID-19). Cytokine storm is characterized by rapid elevation of an inflammatory circulating cytokine such as interleukin-6 (IL-6) and IL-1. However, according to evidence, genetic variables may affect the development and course of infectious diseases. Multiple genetic polymorphisms, mostly single-nucleotide polymorphisms (SNPs), have been linked to this setting's predisposition to viral infections. This study aimed to determine the frequency distribution of IL-6 SNPs rs1800795 and IL-1β SNPs rs16944 and rs1143627 gene polymorphisms and their association with the clinical severity of COVID-19 patients in Surakarta, Indonesia. This study aims to determine the association between IL-6 rs1800795 and IL-1β rs16944 with COVID-19 clinical severity.

Methods: This study used a cross sectional design conducted at Universitas Sebelas Maret Hospital and centralized isolation of the Donohudan Hajj Dormitory from May to November 2021. A total of 120 COVID-19 patients were divided into 3 groups: asymptomatic, mild-moderate, and severe-critical. The detection of IL-6 SNPs rs1800795 and IL-1β SNPs rs16944 was carried out by quantitative PCR (qPCR) examination, and IL-6 and IL-1β were determined by the ELISA method.

Result: There was no significant association between IL-6 SNPs rs1800795 (p=1.000) and IL-1β SNPs rs16944 (p=0.119) with clinical severity. In IL-1β SNPs rs16944 gene polymorphisms, the GG genotype was more commonly found in the asymptomatic group. AG genotype was commonly found in the symptomatic group (mild to critical). There was a significant association between IL-1β levels and clinical severity (p=0.03), whereas the association between IL-6 levels and clinical severity is not significant (p=0.103).

Conclusion: There was a correlation between IL-1β levels with clinical severity. In IL-1β SNPs rs16944, the GG genotype may act as a protective factor, whereas the AG genotype may act as a factor that increases the clinical severity of COVID-19.

Keywords: COVID-19, clinical severity, IL-6 and IL-1β, gene polymorphisms.
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INTRODUCTION

Coronavirus disease 2019 is caused by a new highly pathogenic virus called SARS-CoV-2 and severe acute respiratory syndrome.[1] Flu-like conditions and symptoms. However, infected patients could become critically ill, resulting in death. ARDS, pneumonia, and multiple organ failure are believed to be some of the severe clinical manifestations of COVID-19 progression.[2] Severe COVID-19 presents most commonly as ARDS with hypoxic respiratory failure. In this condition, overexpression of pro-inflammatory cytokines such as IL-6 can cause endothelial dysfunction and damage vital organs, especially the lung.[3]

A background of severe illness progression is created by impaired SARS-CoV-2 clearance due to genetic and viral features, decreased interferon levels, increased neutrophil extracellular traps, enhanced pyroptosis, and compounded by cytokine storm, among other recognized mechanisms.[4] The wide range of symptoms and severity of the illness experienced by people of different nationalities and geographical places is one of its most noticeable characteristics. Effective management of COVID-19 in humans requires serological response evaluation, analytical techniques for SARS-CoV-2 testing, and identification of groups at risk. Understanding the variations in common diseases' severity and population records is critical.[1]

In COVID-19, many background gene mutations may increase the risk of severe disease progression and the emergence of a cytokine storm.[4] It is thought that genetic variables affect a person's susceptibility to SARS-CoV-2 infection. The fact that COVID-19 is linked to an elevated mortality risk in men and some ethnic groups shows that the host's genetic characteristics can affect a person's mortality risk. The severity of COVID-19

and its onset is correlated with age over 60, male sex, and concomitant metabolic illnesses. Genetic variations affect how infectious diseases progress. It has been suggested that several genetic variants, mostly SNPs, predispose this environment to viral infection. The human genetic variety most likely has an impact on the immune system. Pro-inflammatory pathways were implicated, but the precise relevance role of gene structure in SARS-CoV-2-related illness states was inadequately investigated until recently. By applying precision medicine techniques to prevent and clinically monitor the disease, identifying host genetic components linked to SARS-CoV-2 disease may make it easier to develop novel treatments for the illness.[5]

High amounts of circulating inflammatory cytokines are present in COVID-19 patients.[6] Monocytes and macrophages make up the majority of inflammatory cells invading the lung, which may account for the higher levels of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α.[4] These findings imply hypercytokinemia, a characteristic of COVID-19. It is possible to discriminate between mild, moderate, and severe instances of mainly IL-1 and IL-6, but only at certain serum concentrations of these cytokines.[6] "Immunogenetic profiling" refers to the foundation and significance of SNPs linked to immune responses. It has been suggested that SARS-COV-2 infection and IL-6 polymorphisms are related. The IL-6 rs1800795 G allele has been shown to play a protective role in pneumonitis-induced sepsis.[7]

This study aimed to determine the frequency distribution of gene polymorphisms SNP IL-6 rs1800795 and IL-1β rs16944 and to find a correlation between the gene polymorphisms SNP IL-6 rs1800795 and IL-1β rs16944 with clinical severity of COVID-19 patients in Surakarta. We hope this study can add to the COVID-19 gene polymorphisms database in Indonesia, which is useful for further research on gene polymorphisms in COVID-19 patients and guides in more specific management of severe COVID-19 patients according to the gene polymorphisms.

METHODS

This research was a cross sectional study with purposive technique sampling. This study was conducted at the UNS Hospital Sukoharjo and Centralized Isolation Donohudan Dormitory Boyolali, Central Java, from May to November 2021.

Population and Sample

This study involved 120 COVID-19 patients with mild to critical severity hospitalized in the COVID-19 ward UNS hospital, while asymptomatic patients underwent centralized isolation in Hajj dormitory, Donohudan, Boyolali, Central Java. Informed consent was obtained before data collection and signed by patients/families willing to participate in the study. The population of this study was divided into three groups based on clinical degrees: asymptomatic group, mild-moderate symptom group, and severe-critical symptom group. Each group of consist 40 patients.

Research subjects must meet the inclusion criteria, namely: patients with confirmed COVID-19 patients with a positive PCR examination, age >18 years old, willing to participate in the study, and have comorbidities with a Charlson comorbidity index (CCI) score ≤3. Most comorbidity found were diabetes mellitus, hypertension, hypertensive heart disease, and chronic obstructive pulmonary disease.

Demographic data such as age, gender, clinical symptoms, vital sign, and comorbidities were collected in this study. Blood samples were taken when patients entered the emergency room/ hajj dormitory Donohudan; 6 mL collected blood was divided into two tubes: 3cc of EDTA blood for DNA extraction purposes, and 3 mL was stored in a serum tube for centrifugation for serum IL-6 and IL-1β examination. The blood samples were stored in a -80 °C freezer during the data collection process. Blood gas analysis was performed on severe and critical patients, and a chest X-ray was performed on patients treated at UNS hospital. Serum IL-6, IL-1β level and DNA extraction were carried out at the Biomedical laboratory of the Faculty of Medicine, Universitas Sebelas Maret Surakarta. DNA extraction was sent to the Genetica Science Indonesia Laboratory, Tangerang, Indonesia, to be examined for gene polymorphism using qPCR.

Measurement of serum IL-6 and IL -1β

Blood samples were collected from an antecubital vein into a serum tube, then centrifuged to get the serum. IL-6 and IL-1β levels were measured using enzyme-linked immunosorbent assay (human ELISA kit, Invitrogen, Thermo Scientific brand). Material needed for serum IL-6 examination includes Biotinylated Antibody reagent, Streptavidin-HRP solution, TMB substrate, stop solution, and plate reader. Material needed for serum IL-1β examination includes: capture antibody, antigen, biotin conjugate, streptavidin-HRP, and stop solution.

DNA Extraction and Genotyping

DNA extraction was performed on up to 300µL of fresh whole blood per sample using the Geneaid Genomic DNA Mini Kit (blood/cultured cells) according to the manufacturer's instructions. Four steps for DNA extraction include sample preparation (fresh whole blood up to 300µL), cell lysis, DNA binding, washing, and DNA elution. DNA extraction samples were genotyped using Thermo Fisher Scientific for polymorphic IL-6 SNP gene rs1800795 and IL-1β SNP gene rs16944. The primers were design by Integrated DNA Technologies (https://www.idtdna.com/site/order/designtool/) are listed in Table 1. The qPCR examination protocol consists of 6 stages: sample DNA was prepared, master mix and reporter mix were combined, SNP genotyping assay was prepared, PCR examination was carried out, data was collected and analyzed, and data were analyzed for triallelic assays.

Statistical Analysis

Statistical analysis was performed using the SPSS 22 software package (IBM, Chicago, IL). The frequency distribution of allelic genotyping in the population is described in percentages (%), while the levels of IL-6 and IL-1β based on clinical severity are described in mean (standard deviation). Statistical analysis using Pearson Chi-Square to find the association between gene polymorphisms with clinical

severity, Rho Spearman Rank to find the association between gene polymorphisms with cytokine level, and Mann Whitney to find differences in cytokine levels in IL-6 and IL-1β gene polymorphisms. Statistically significant if p<0.05.

Table 1. DNA samples were genotyped by using a Taqman commercial primer.

Gene (reference SNP)	Primers	
IL-1β (rs16944)	Allele Primer 1	/rhAmp-F/TGCTGTTCTCTGCCTCArGGAGC/GT1/
	Allele Primer 2	/rhAmp-Y/TGCTGTTCTCTGCCTCGrGGAGC/GT1/
	Locus primer	GCTGGTCTTGCAGGGTTGTrGTGAG/GT3/
IL-6 (rs1800795)	Allele Primer 1	/rhAmp-F/ATGTGACGTCCTTTAGCATGrGCAAG/GT4/
	Allele Primer 2	/ rhAmp-ATGTGACGTCCTTTAGCATCrGCAAG/GT4/
	Locus primer	GCGAAAGTAAAGGAAGAGTGGTTCTGrCTTCT/GT1/

Table 2. Frequency distribution of IL-6 and IL-1β gene polymorphisms on the clinical severity of COVID-19.

Variable	IL-6 rs1800795		IL-1β rs16944		
	GG n (%)	CG n (%)	GG n (%)	AA n (%)	AG n (%)
No symptom	40 (33.6%)	0 (0.00%)	12 (22.6%)	13 (54.2%)	15 (34.9%)
Mild-moderate	39 (32.8%)	1 (100%)	19 (35.9%)	6 (25.0%)	15 (34.9%)
Severe-critical	40 (33.6%)	0 (0.00%)	22 (41.5%)	5 (20.8%)	13 (30.2%)

Table 3. Correlation between IL-6 and IL-1β gene polymorphisms with clinical severity of COVID-19 patients.

Variable	Clinical severity			P value
	No symptom n (%)	Mild-Moderate n (%)	Severe-Critical n (%)	
IL-6 rs1800795				
GG	40(33.6%)	39(32.8%)	40 (33.6%)	0.365
CG	0(0.0%)	1(100.0%)	0(0.0%)	
IL-1β rs 16944				
GG	12(22.6%)	19(35.8%)	22(41.5%)	0.095
AA	13 (54.2%)	6 (25,0%)	5(20.8%)	
AG	15(34.9%)	15(34.9%)	13(30.2%)	

Table 4. Differences in IL-6 and IL-1β levels in gene polymorphisms IL-6 rs1800795 and IL-1β rs16944 in COVID-19 patients.

Gene, SNP	Genotype	Level (mean)	P value
IL-6 rs1800795	GG	36.15±66.94	0.733
	CG	16.62±0.00	
IL-1β	GG	4.57±4.97	0.046*
	AG	3.37±4.39	
	AA	6.84±4.48	

Note: *p value <0.05

Table 5. Correlation between IL-6 and IL-1β levels with clinical degree COVID-19 patients.

Variable	Clinical Degree			p-value
	No symptom	Mild-Moderate	Severe-Critical	
IL-6	17.01±5.27	33.79±76.16	57.15±9.12	0.103
IL-1β	5.27±4.28	3.51±5.55	9.12±4.58	0.003*

Note: *p value <0.05

RESULT

The genotype distributions of the selected SNPs of IL-6 rs1800795, IL-1β rs16944, and IL-1β rs1143627 and their associations with the clinical severity of the disease are displayed in Table 2.

In the IL-6 SNPs rs1800795, the GG genotype was found in 119 patients, namely 33.6% in the no-symptom group, 32.8% in the mild-moderate symptom group, and 33.6% in the severe-critical group. Only one patient with a CG genotype was in the mild-moderate group (100%). For the IL-1β SNP rs16944, the GG genotype was found in 53 patients, 22.6% in the asymptomatic group, 35.9% in the mild to moderate symptom group, and 41.5% in the severe to moderate symptom group. The AA genotype was found in 24 patients, 54.2% in the asymptomatic group, 25.0% in the mild-moderate group, and 20.8% in the severe-critical group. The AG genotype was found in 43 patients, 34.9% in the asymptomatic group, 34.9% in the mild-to-moderate group, and 30.2% in the severe-to-severe group. From the IL-1β SNPs rs16944 distribution, it can be seen that the GG genotype was more commonly found in the symptomatic group (mild to critical), the AA genotype was more commonly found in the asymptomatic group, while the AG genotype was equally distributed in the three groups.

Analysis of the correlation between IL-6 and IL-1β gene polymorphisms with clinical severity is shown in Table 3. There is no correlation between IL-6 SNPs rs1800795 GG and CG genotype with the clinical severity of the disease (p = 0.365). No correlation was also found between gene polymorphisms IL-1β SNPs rs16944 GG, AA, and AG genotype with clinical severity (p = 0.095).

The mean level of IL-1β rs16944 gene polymorphisms GG genotype was 4.57±4.97, the AG genotype was 3.37±4.39, and the AA genotype was 6.84±4.48. The analysis obtained significant results with a P value of 0.046 (P<0.05). The mean level of IL-6 rs1800795 gene polymorphisms GG genotype was 36.15±66.94, and the CG genotype was 16.62±0.00, statistically

not significant with p value 0.733 (p>0.05). Differences in IL-6 and IL-1β levels with IL-6 rs1800795 and IL-1β rs16944 gene polymorphisms are shown in Table 4.

The measurement of biochemical markers (IL-6 and IL-1β serum) showed that the mean of IL-6 levels was 17.01 ± 5.27 in the asymptomatic group, 33.79 ± 76.16 in the mild to moderate group and 57.15 ± 9.12 in the severe to the critical group. There was no correlation between IL-6 levels and clinical severity (p=0.103). Whereas the mean of IL-1β level in the no-symptom group was 5.27±4.28, the mild-moderate group was 3.51±5.55, and the severe-critical group was 9.12±4.58. There was a correlation between the IL-1β value and with patient's clinical severity (p = 0.003). The mean cytokine level association with clinical severity is shown in Table 5.

DISCUSSION

The first known case of the SARS-CoV-2 virus occurred in Wuhan, China, in December 2019. It is a type of human coronavirus (HCoV) that is extremely dangerous to public health and causes zoonotic diseases.[10] Individuals with COVID-19 experience different clinical signs. A minority of individuals develop severe COVID-19, including ARDS and systemic inflammation, while most patients have minimal or no disease.[8,9]

The variability in the severity of COVID-19 can be explained by many factors, including epidemic control measures and medical resources in different countries, as well as the individual's age, gender, and comorbidities. In addition, an individual's genetic background may also influence her susceptibility to COVID-19, particularly genetic variants that explain different immune responses to coronavirus. IL-6 plays a key role in enhancing the inflammatory response in SARS-CoV-2 infection.[9] Elevated serum levels of IL-6, IL-1 and TNF-α occur during cytokine storms.[3] IL-6 and other cytokines are hallmarks of severe COVID-19. IL-6 expression is strongly influenced by a promoter and regulatory region polymorphisms. Some of these SNPs vary significantly between ethnic populations and are associated with differential responses to various pathogens.[9]

This study showed no correlation between polymorphisms of IL-6 SNPs rs1800795 GG and CG genotype with clinical severity of COVID-19 patients. This result is in accordance with the study conducted by Falahi S et al., 2022 in Iranian COVID-19 populations. The frequency of the G allele and GG genotype was higher in the mild and severe groups than in the C allele and CG genotype.[1] In this study, the GG genotype was higher in all groups but not statistically significant. However, these results are not in accordance with the previous study by Kerget F et al., 2021, which showed that IL-6 rs1800795 polymorphisms were associated with the clinical severity of COVID-19 patients in Turkey. The GG genotype was more common and statistically significant in the macrophage activation syndrome (MAS) group. The G allele was significantly higher in the MAS group, a risk factor for elevated IL-6 levels and progression to MAS.[3] In contrast to studies conducted by Rahimlou B et al., 2022, the G allele was found to be a protective factor against COVID-19.[12] Another study found that the IL-6 promoter SNP rs1800795 protected White Spanish patients from pneumococcal pneumonia, but the G-G alleles at rs1800795 favor a worse evolution on chronic HCV infection in Italians and also confer susceptibility to human papillomavirus (HPV)-associated cervical cancer in North Indians.[9]

This study's IL-1β SNPs rs16944 gene polymorphisms showed that GG genotypes dominated in the symptomatic group (mild to critical), whereas AA genotype dominated in the asymptomatic group, but not statistically significant. From the distribution results, the AG genotype possibly is a protective factor against COVID-19 symptoms, while the GG genotype is possibly associated with an increase in the clinical severity of COVID-19. A previous study by Ramirez R et al. 2015 found that the IL-1β SNP rs16944 genetic polymorphism was associated with a reduced risk of H1N1 infection. G alleles associated with protection against H1N1 infection.[11] Study by Kesharvarz M et al., 2019 showed that the IL-1β SNPs rs16944 gene polymorphisms, AA genotype, significantly increased the risk of experiencing influenza, while influenza B infection was protective.[12] Study by Rogo et al., 2016 showed that the IL-1β SNPs rs16944 gene polymorphisms of the AA genotype versus GG/AG genotype increase susceptibility to invasive flu A (H3N2) and mild infection after solid organ transplantation.[13]

In this study, gene polymorphisms of IL-6 SNP rs1800795 did not exhibit a correlation with IL-6 levels. The GG genotype had higher levels of IL-6 than the CG genotype. This result was in accordance with Kerget F et al., 2021 state that IL-6 levels had a higher increase in the GG genotype than the GC genotype. In the IL-6 rs1800795 analysis, a significant positive correlation between G allele frequency with patient's IL-6 levels and MAS prevalence may prove that the G allele is important for IL-6 synthesis.[3] IL-6 levels are elevated in COVID-19 patients and correlate with disease severity. The IL-6 rs1800795 (174G/C) polymorphism has been shown to affect IL-6 levels, with Indians (especially North Indians) having a lower frequency of the C allele than Caucasians, resulting in IL-6 could be less production in Indian.[14]

In this study, IL-6 levels were independent of COVID-19 severity. The level of IL-6 did not differ between mild-to-moderate and severe-to-severe groups. This condition may occur because of persistent viral infection, causing CD8T and CD4 T cell exhaustion, triggering poor production of effector cytokines and high expression of PD-1. Influenza infection does not result in long-term viral persistence, whereas acute viral infection depletes CD8 T cells.[15] Covid-19 infection in which T-cell depletion induces aberrant immune responses such as lymphocyte cytokine storm and responsive cytokine depletion.[16] Other factors that significantly affect the clinical severity of COVID-19 include obesity exposure to cigarette smoke, high LDH serum albumin and lymphopenia <900/mm^3.[17] However, all these factors were not analyzed in this study.

This study found a significant association between IL-1β levels with clinical severity and significant differences in IL-1β levels in AA, GG, and AG genotype gene polymorphisms of IL-1β rs16944. The severe clinical severity of

COVID-19 increases the production of pro-inflammatory cytokines such as IL-1β in monocytes/macrophages. IL-1β is a pro-inflammatory cytokine activated and secreted by inflammasomes in the peripheral blood and bronchoalveolar lavage fluid of COVID-19 patients who developed pneumonia.[18] IL-1β works convincingly, promoting an exaggerated immune response.[17]

Limitations of this study include that the study was conducted in one region/race and the uncomplicated. It included a lack of control when healthy people were infected with COVID-19.

CONCLUSION

The IL-1β SNP rs16944 polymorphism, AG genotype possibly is a protective factor against symptomatic COVID-19 development, and GG genotype possibly is a factor that increases symptom onset and clinical severity of COVID-19. There is a significant association between serum IL-1β levels with clinical severity and a differences serum IL-1β levels in IL-1β rs16944 gene polymorphisms in COVID-19 patients.

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CONFLICT OF INTEREST

The author reports no conflict of interest in this work.

ETHICAL CLEARANCE

This study was approved by the Faculty of Medicine ethics committee, Universitas Sebelas Maret number: 90/UN27.06.6.1/KEP/EC/2021.

AUTHOR CONTRIBUTION

HA and BS contribute to study concepts and design, defining intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscripts review, and as a guarantor of this study. R and TDA contribute to study concepts and design, defining intellectual content, clinical studies, data acquisition, data analysis, manuscripts review, and as a guarantor of this study. DP and HN contribute to literature searches, clinical studies, data acquisition, statistical analysis, manuscript preparation, and editing.

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