ORIGINAL ARTICLE

Association of IL-6 rs1800796 Gene Polymorphism on Susceptibility to Pulmonary Tuberculosis

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ABSTRACT

Introduction: IL-6 is a pro-inflammatory cytokine controlling the immune response to TB. This study investigated the association of IL-6 rs1800796 gene polymorphism on susceptibility to pulmonary TB.
Methods: The case-control study involved 71 cases and 34 controls. Blood samples were taken from all study participants at Dr. Saiful Anwar General Hospital, Malang, between August 2020 and February 2021. Blood samples were used in a genotyping investigation to determine SNPs using the PCR-Multiplex technique.
Results: The genotype association of IL-6 rs1800796 (G/G, G/C, C/C) and allele frequency for patients and controls of IL-6 rs1800796 with susceptibility to pulmonary TB were insignificant ($p > 0.05$).
Conclusion: This study found no evidence of an association of IL-6 rs1800796 gene polymorphism with susceptibility to pulmonary TB.

INTRODUCTION

In developing nations, tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains a leading cause of death and morbidity, although most of it can be cured and prevented. Since 1980, the incidence of TB and mortality rates have increased rapidly. From World Health Organization (WHO) Global TB Report 2020, there were approximately 10 million new TB cases in 2019, with 2.9 million of those not being diagnosed or reported to the WHO. Human immunodeficiency virus (HIV) negative deaths were 1.2 million people, and cases of HIV positive were 208,000.[1]

The highest number of cases were found in Southeast Asia (44%), Africa (25%), and the West Pacific region (18%). India (26%), Indonesia (8.5%), China (8.4 %), Philippines (6%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%), and South Africa (3.6%) are the eight nations with the most TB cases (which account for ⅔ of global TB cases) (3.6%). HIV was found in 8.2% of TB cases. With an absolute total of 465,000 (400,000 – 535,000) new cases, 3.3% of new pulmonary TB cases and 18% of pulmonary TB with a history of previous TB treatment were predicted to be multidrug-resistant (MDR) or rifampicin-resistant (RR) TB in 2019.

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Following India, Indonesia is the world's second-highest number of TB cases. 19,000 out of estimated 845,000 new TB cases in Indonesia in 2019 were TB-HIV positive cases. There was an estimation of 92,000 deaths in TB-HIV negative cases and 4,700 deaths in TB-HIV positive patients.[1] TB control strategy in Indonesia (2020-2024) is implemented to achieve a decrease of the incidence—from 319 per 100,000 population in 2017 to 190 per 100,000 population—and death rate—from 42 per 100,000 population in 2017 to 37 per 100,000 population—of TB in 2024.[2]

The global commitment to exterminate TB stated in the "End TB Strategy"—a component of the Sustainable Development Goals—with one goal, i.e. to end TB epidemic throughout the world. By 2030, the Strategy aims to achieve a 90% decrease in TB mortality compared to 2015, a 95% reduction in TB deaths by 2035, an 80% reduction in TB incidence in 2035 compared to 2015, and no household catastrophic expenditure due to TB in 2030. The target of the national TB control program is the elimination of TB in 2035 and to become TB-free in 2050. The elimination of TB in question is to achieve a coverage of TB cases of 1 case per 1 million population. The "End TB Strategy" emphasizes that the target is expected to be achieved through innovations—such as developing vaccines and TB drugs with short-term regimens.[1,2]

Due to the advent of multidrug-resistant (MDR) and almost extended drug-resistant (XDR) strains of MTB, the global TB situation continues to deteriorate. The continuous spread of HIV among TB patients has given the disease a new dimension.[3] Interestingly, although MTB has infected almost ⅓ of the world's population, only 10% of patients infected with MTB will acquire active TB, while 90% will develop latent TB, which might reactivate years later when the host immune system is compromised. The etiologic agent and its immunogenicity, the pathogen's mechanism of resistance, the type of pathogen, the clinical entity's phase, concomitant infection and bacterial infestation, the host's genetic condition, and the immune system's insufficiency and sufficiency, among other factors, can all affect the immune response in various pathologies.[4,5]

Previous genetic association studies have identified several host genetic loci that significantly contribute to TB susceptibility. The effect of genetic factors can also be seen from the difference in the incidence of TB if it is based on race, ethnicity, and family.[6]

Uncovering the mechanisms underlying genetic variation that influence TB susceptibility or resistance could lead to a better understanding of TB pathogenesis and the development of novel TB prevention and treatment strategies. To control MTB infection in the host, both innate and adaptive immune responses are required. As a result, susceptibility to TB is linked to genetic polymorphisms in molecules involved in innate host defense systems, such as vitamin D receptors, Toll-like receptors (TLR1/TLR6), cytokines and chemokines, and their receptors.[4]

IL-6 is a pro-inflammatory cytokine produced by fibroblasts, monocytes, and endothelial cells that can promote B and T lymphocytes while also controlling the immunological response to TB. This is important for generating the protective Th1 immune response required to resist MTB infection.[7] IL-6 gene polymorphisms had previously been found to be strongly related to various disorders, including heart disease, sepsis, and SLE, in which the gene has a significant role in pathogenesis.[8–10] IL-6 gene is found on chromosome 7p21 and consists of 6 exons with a coding length of 1.3 kb (6119 base pair size). The promoter region of the IL-6 gene has gotten a lot of attention since it has a lot of polymorphisms, including the -572 G/C variant (NCBI ID: rs1800796).[11]

Based on the previously mentioned theory, this study thus analyzed the presence of IL-6 rs 1800796 gene polymorphisms to determine the presence of genetic influences which affect the susceptibility of pulmonary TB disease in sensitive or drug-resistant (DR) patients. Many epidemiological studies have been undertaken to look into the association between IL-6 gene polymorphisms and the risk of TB, however, the results vary. The disparity in results could be explained by the small sample size used in prior studies and the limited effect of the TB risk polymorphism.[11] This study aimed to investigate the association of IL-6 rs1800796 gene polymorphism on susceptibility to pulmonary TB.

METHODS

This study used a case-control study research design. It was conducted from June 2020 to July 2021 on pulmonary TB patients treated at the pulmonary polyclinic or inpatient room at Dr. Saiful Anwar Regional General Hospital, Malang. Patients diagnosed with pulmonary drug-sensitive (DS) or DR TB, aged 18 to 70 years old, who were willing to participate in the study and completed an informed consent form were included in the case group in this study. The control group in this study had to be between 18 and 70 years old, had no clinical signs of pulmonary TB, had no prior history of TB, had normal chest X-ray pictures, and signed an informed consent form. Patients with HIV-AIDS, chronic renal failure, autoimmune diseases, and pregnant patients were not included in this study. The minimum number of samples

was 26 people from each group. Samples were obtained by the means of consecutive sampling within the inclusion and exclusion criteria and were examined for the polymorphism of IL-6 gene rs1800796 using multiplex PCR.

Data processing and analysis were performed using SPSS version 26. The correlation between polymorphism and pulmonary TB susceptibility was analyzed using the chi-square test, with a confidence degree of 95%, $\alpha = 0.05$—the result is meaningful if $p <$ 0,05. To determine the magnitude of the risk factor, odds ratio (OR) was used. This study was approved by the Health Research Ethics Comission, Dr. Saiful Anwar General Hospital, Malang (No. 400/130/K.3/302/2021).

RESULTS

During the study period, we obtained 105 subjects who met the inclusion and exclusion criteria and were willing to participate in the study by signing informed consent. The subjects were divided into 3 study groups—34 subjects in the healthy control group (non-TB) and 71 subjects in the pulmonary TB case groups. The pulmonary TB case groups consisted of 31 subjects with DS-TB and 40 subjects with DR-TB. The sociodemographic characteristics of the research subjects can be seen in Table 1.

The characteristics of the research subjects in this study had the average age of 33.79 ± 4.98 years old in the healthy or non-TB group, 40.42 ± 14.09 years old in DS-TB group, and 45.5 ± 13.06 years old in DR-TB group. For the age variable, a normality test was performed using the Shapiro-Wilk test. If the p-value is more than 0.05 ($p > 0.05$), the variable passed the test and was normally distributed. The results of the normality test for the age variable, however, had a p-value of 0.000 ($p < 0.05$), indicating that the normality of the data was not met. Furthermore, the Kruskal Wallis test yielded a p-value of 0.001 ($p < 0.05$), demonstrating that there was a significant difference in age characteristics in the 3 groups, where the non-TB control group had a younger average age than the TB case group. The control group had 58.8% males, 48.4% in DS-TB group, and 60% in DR-TB group. The Chi-Square test obtained a p-value of 0.577 ($p > 0.05$), thus proving that there was no gender difference between the 3 groups.

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The control group had 58.8% males, 48.4% in DS-TB group, and 60% in DR-TB group. The Chi-Square test obtained a p-value of 0.577 ($p > 0.05$), thus proving that there was no gender difference between the 3 groups. The average BMI of the non-TB control group was 22.86 ± 2.86, 18.55 ± 3.89 in DS-TB group, and 18.5 ± 3.04 in DR-TB group. The normality test using the Shapiro-Wilk test yielded a p-value of 0.033 ($p < 0.05$), indicating that the normality of the data was not met. The Kruskal-Wallis test was then performed and resulted in a p-value of 0.000 ($p < 0.05$), which proved that there was a significant difference in BMI characteristics in the 3 study groups, where TB groups—both DS- and DR-TB—had a lower average BMI compared to the non-TB control group.

Table 1. Sociodemographic characteristics of the research subjects

Characteristic		Control non-TB (n = 34)	TB positive		p-value
			DS-TB (n = 31)	DR-TB (n = 40)	
Age	Minimum	29	19	18	0.001[a]
	Maximum	58	69	69	
	Mean ± SD	33.79 ± 4.98	40.42 ± 14.09	45.5 ± 13.06	
Sex	Male	20 (58.8%)	15 (48.4%)	24 (60%)	0.577[b]
	Female	14 (41.2%)	16 (51.6%)	16 (40%)	
BMI	Median	19.3	13.8	12.1	0.000
	Minimum	31.1	29.9	26.1	
	Mean ± SD	22.86 ± 2.86	18.55 ± 3.89	18.5 ± 3.04	

a Kruskal Wallis Test ; b Chi Square Test

The examination of IL-6 rs 1800796 Gene Polymorphism in this study was performed using the multiplex PCR method which showed appropriate pieces of DNA bands (100bp marker) with a reading on 2% agarose gel.

The visible products of this method were GG, CC, and GC genotypes. Each genotype contained 2 alleles (diploid chromosomes). GG genotype had 2 G alleles, CC genotype had 2 C alleles, and GC genotype had 1 G allele and a C allele.

The description of the allele frequency and genotype of IL-6 rs1800796 gene polymorphism in the non-TB control group compared to TB groups is shown in Table 5.4. The comparison between the control group and DS- and DR-TB groups is shown in Table 5.5. The comparison of allele frequencies and genotypes of IL-6 rs 1800796 gene polymorphism was performed using the Chi-Square test.

According to Table 2, the frequency of G allele in the control group was 19 (55.9%) and 49 (69%) in TB group. The frequency of G allele was found more in TB case groups than in the non-TB group. The Chi-Square test obtained a p-value of more than 0.05 ($p > 0.05$), proving that there was no significant difference in the frequency of G allele between TB and non-TB groups. Likewise, the comparison test obtained a p-value of more than 0.05 ($p > 0.05$), which proved that there was no significant difference in the frequency of C allele. The results of the comparison test for GG Genotype p-value were more than 0.05. The comparison of the genotype frequencies of GC and CC between each group also yielded a p-value of more than 0.05 ($p > 0.05$), proving that the genotype frequencies of GG, GC, and CC were not significantly different between non-TB and TB groups.

As could be seen in Table 3, the frequency of G allele in the control group was 19 (55.9%), was 20 (64.5%) in DS-TB group, and 29 (72.5%) in DR-TB group. The frequency of G allele was found more in DR-TB case group. The Chi-Square test yielded a p-value of more than 0.05 ($p > 0.05$) in all comparisons.

Table 2. Comparison of allele and polymorphic genotype of IL-6 on non-TB and TB groups

Variable	Group		p-value	OR (95% CI)
	Non-TB control	TB		
GG	3 (8.8%)	6 (8.5%)	0.949	1.05 (0.25-4.47)
GC	16 (47.1%)	43 (60.6%)	0.192	0.58 (0.25-1.32)
CC	15 (44.1%)	22 (31%)	0.187	1.76 (0.76-4.09)
Allele G	19 (55.9%)	49 (69%)	0.187	0.57 (0.24-1.32)
Allele C	31 (91.2%)	65 (91.5%)	0.949	1.05 (0.25-4.47)

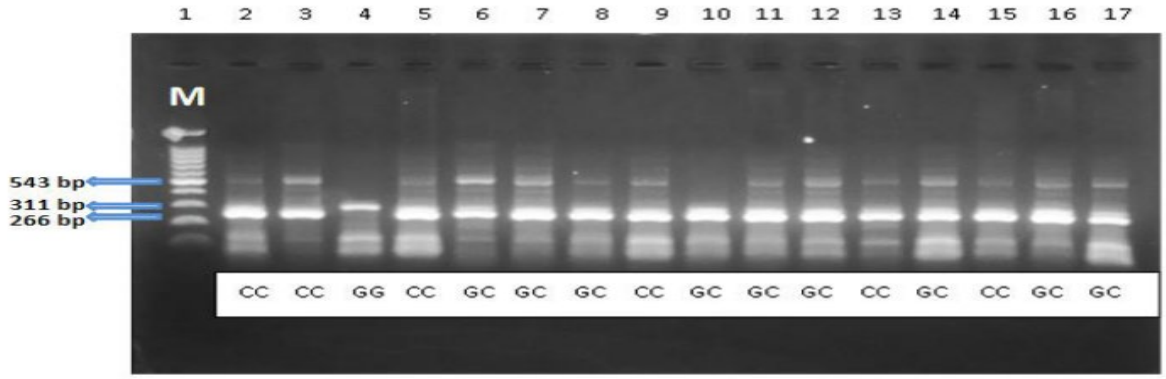

Figure 1. The electrophoresis of multiplex polymorphic IL-6 rs 1800796 gene. M = marker 100bp. Genotype GG: if the strain shows on 311, 543bp; genotype GC = 266, 311, 543bp; genotype CC = 266, 543 bp.

Table 3. Comparison of alleles and genotypes of IL-6 gene polymorphism rs1800796 in non-TB control group and DS-TB and DR-TB groups

Variable	Non-TB control	TB positive		p-value		
		DS-TB	DR-TB	Non vs DS-TB OR(95%CI)	Non vs DR-TB OR(95%CI)	DS- vs DR-TB OR(95%CI)
GG	3 (8.8%)	3 (9.7%)	3 (7.5%)	0.905 0.9 (0.17-4.85)	0.835 1.19 (0.22-6.34)	0.744 1.32 (0.2-7.05)
GC	16 (47.1%)	17 (54.8%)	26 (65%)	0.531 0.73 (0.28-1.94)	0.121 0.48 (0.19-1.22)	0.385 0.65 (0.25-1.71)
CC	15 (44.1%)	11 (35.5%)	11 (27.5%)	0.478 1.44 (0.53-3.9)	0.136 2.08 (0.79-5.49)	0.471 1.45 (0.53-3.99)
Allele G	19 (55.9%)	20 (64.5%)	29 (72.5%)	0.478 0.7 (0.26-1.89)	0.136 0.48 (0.18-1.27)	0.471 0.69 (0.25-1.9)
Allele C	31 (91.2%)	28 (90.3%)	37 (92.5%)	0.905 0.9 (0.17-4.85)	0.835 1.19 (0.22-6.34)	0.744 1.32 (0.25-7.05)

Table 4. Correlation test between IL-6 rs1800796 polymorphic gene of the non-TB and TB groups

Variable		Non-TB Control	TB	p-value	OR	95%CI
Genotype	GG	3 (8.8%)	6 (8.5%)	(Reff)		
	GC	16 (47.1%)	43 (60.6%)	0.699	1.344	0.300-6.023
	CC	15 (44.1%)	22 (31%)	0.691	0.733	0.158-3.398
Allele G		19 (55.9%)	49 (69%)	0.187	0.569	0.245-1.322
Allele C		31 (91.2%)	65 (91.5%)	0.949	1.048	0.246-4.471

As proven by this test, there was no significant difference in the frequency of G allele between the control and TB positive groups. The comparison of the frequency of C allele between the control group and TB groups obtained a p-value of more than 0.05 ($p > 0.05$), proving that there was no significant difference in the frequency of C allele.

The comparison test for GG genotype yielded a p-value of more than 0.05 ($p > 0.05$) in all comparisons. Likewise, the comparison of the frequency of GC and CC genotypes between groups obtained a p-value of more than 0.05 ($p > 0.05$). This clearly showed that the genotype frequencies of GG, GC, and CC in the non-TB control group, DS- or DR-TB were not significantly different.

A correlation test between IL-6 rs 1800796 gene polymorphism with susceptibility to pulmonary TB can be performed using the Chi-Square test and calculating OR value. Table 4 shows the correlation test between IL-6 Gene Polymorphisms with susceptibility to pulmonary TB where GG genotype was used as a reference.

The p-value for the correlation between GC genotype and susceptibility to pulmonary TB was 0.699 ($p > 0.05$), indicating that there was no significant correlation between GC genotype and susceptibility to pulmonary TB (OR = 1.344 (0.3–6.032)). Likewise, CC genotype obtained a p-value of 0.691 ($p > 0.05$), which indicated no significant correlation between CC genotype and susceptibility to pulmonary TB.

The correlation test between G allele and susceptibility to pulmonary TB yielded a p-value of 0.187 ($p > 0.05$) and OR = 0.569 (0.245-1.322), which proved that there was no significant correlation between both variables. Likewise, the correlation test between C allele and susceptibility to pulmonary TB yielded a p-value of 0.949 ($p > 0.05$), indicating that there were no significant correlations.

DISCUSSION

There was no significant difference in the frequency of GG, GC, CC genotypes, G and C alleles between non-TB control group, DS-TB group, and DR-TB group ($p > 0.05$) in this study. According to a study conducted in the Iraq province of Babylon, GC genotype was more closely associated with pulmonary TB, but GG genotype was associated with lower susceptibility to the risk of pulmonary TB in carrier individuals.[4] A study by Zhang, *et al.* (2012) in the Chinese population also found that GG genotype was associated with a reduced risk of TB infection.[4] On the other hand, a meta-analysis study by Wang, *et al.* (2017) suggested that GG genotype was linked to a higher risk of pulmonary TB than GC and CC genotypes. However, more research was required to investigate the mechanism by which IL-6 Gene Polymorphism regulates IL-6 production and plays a role in pulmonary TB susceptibility.[7] Sun and Wang (2017) also found that having CC genotype was linked to a decreased incidence of pulmonary TB.[11] There was no significant difference in the percentages of G allele, C allele, GG, GC, and CC genotypes between DS- and DR-TB groups in this study.

This study found that there was no significant relationship between IL-6 rs1800796 gene polymorphism and the susceptibility to pulmonary TB, both from the correlation of G and C alleles and GG, GC, and CC genotypes. A study in the province of Babylon, Iraq showed a significant relationship between IL-6 rs1800796 genotype GC and the susceptibility to pulmonary TB; while there was no significant correlation of the allele frequency between the positive TB group and the control group.[4] In contrast, Zhang, *et al.* (2012) discovered that genetic polymorphisms in the IL-6 promoter, which governed cytokine production, indicated host resistance to pulmonary TB in the Chinese population.[4] Wang, *et al.* (2017) proposed in a meta-analysis that IL-6 rs1800796 gene polymorphism may be associated with a lower risk of TB in Asian populations.[7]

Ethnicity is a significant factor for the risk of TB which, in a meta-analysis by Wang, *et al.*, showed a controversial conclusion—where in Asian and Latino populations, there was a substantial connection between IL-6 gene polymorphism (-174G/C) and TB risk, while no such association was seen in the Caucasian population. This shows that TB risk may be influenced by genetic variables in various ethnic groups. Furthermore, environmental variables can alter TB susceptibility by interacting with gene polymorphisms.

The most effective method for controlling environmental factors on TB risk is still being studied. More research is needed on how IL-6 Gene Polymorphism promotes TB susceptibility and regulates IL-6 production. Furthermore, discrepancies in research design and PCR examination procedures used in each investigation altered the final study outcome.[7]

IL-6 rs1800796 has been linked to vulnerability to inflammatory disorders in the Chinese-Han population, including coronary heart disease, idiopathic membranous nephropathy, type 2 diabetes, and chronic periodontitis, according to several independent genetic investigations. This study discovered that IL-6 rs1800796 is a frequent genetic SNP in this group, increasing vulnerability to a variety of inflammatory disorders, including mycobacterial infections. Many studies have found IL-6 gene polymorphisms to be linked to TB susceptibility, but the results have been mixed. The role of IL-6 in TB still being researched.

LIMITATION

The large numbers of epidemiological studies have been performed to examine the relationship between IL-6 gene polymorphisms and the risk of TB, but different studies reached different conclusions. The differences in results may be due to a possible small effect of the polymorphism on TB risk and the relatively small sample sizes.

CONCLUSION

There was no correlation between allele expression and IL-6 rs 1800796 genotype polymorphic on healthy individuals and DS-TB. There was no correlation between polymorphic IL-6 rs 1800976 gene expressions of non-TB individuals and DR-TB. There was no correlation between allele expression and polymorphic IL-6 rs 1800796 genotype on DS- and DR-TB. There was also no correlation between IL-6 rs 1800796 genotype polymorphic on the susceptibility to TB.

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Conflict of Interest
The author declared there is no conflict of interest.

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Authors' Contributions
Conceiving the study: MK. Designing the experiments, gathering, analyzing, and interpreting the data, making tables and figures, writing the manuscript: YJS, INC, and NS. Reviewing and revising: MK and ASL. All authors contributed and approved the final version of the manuscript.

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