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# Cytokine Level and Symptoms of Schizophrenia

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## Abstract

**BACKGROUND:** The study was intended to find one of the cytokines, that is, tumor necrosis factor (TNF)-alpha correlation with PANSS scores of people with schizophrenia (PwS) and their differences compared to the healthy people of Malayan- Mongoloid Race.

**AIM:** The aim of this study was providing a profile of TNF-alpha level in PwS of Malayan-Mongoloid race and its correlation with positive and negative symptoms in schizophrenia.

**METHODS:** It was conducted using cross-sectional and following sampling methods, with inclusion and exclusion criteria set for the PwS and control groups.

**RESULTS:** The result was no correlation between TNF-alpha levels with PANSS scores on PwS ($p > 0.005$), with very weak correlation and positive correlation direction, and there were differences in TNF-alpha levels.between PwS and control groups.

**CONCLUSION:** It can be concluded that the higher levels of TNF-alpha would impact on the severity symptoms experienced by PwS.

## Introduction

Schizophrenia is a psychotic disorder that has the characteristics of delusions, hallucinations, disorderly behavior, disturbances in thinking, and other negative symptoms. This disease has prevalence in the United States around 0.3–0.7%, yet this figure varies by country, race/ethnicity, or geographical condition of an area. The incidence is higher in men compared to women, especially to negative symptoms and worse disease outcomes [1]. During this time, it is estimated that inflammation and immune system dysfunction have a close relationship with schizophrenia. The inflammatory process and cytokines may have pathogenic importance for the development of schizophrenia both in the process of brain development and in the acute condition of the disease. Cytokines mediate infection, hypoxia, and ischemia in fetal brain development and the relationship between prenatal exposure to infection and the risk of schizophrenia is not limited to one infectious agent. The increased risk of developing schizophrenia is thought to be due to the role of modulation from cytokines. Cytokines are low molecular weight proteins that mediate immune and inflammatory responses and are excreted by glial and neuronal cells in the central nervous system and regulate brain development. Proinflammatory cytokines include, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNF)-alpha. The consequences of prolonged inflammation are often unfavorable, and in the condition of schizophrenia, it will result in chronic and decrease neuropsychiatric conditions over time [2].

One of the cytokines that have an essential role for schizophrenia is TNF-alpha, TNF-alpha level was found to be significantly increased in people with schizophrenia (PwS) compared to healthy people in the control group [3], [4], [5], [6]. Other studies with the same results were also reported by O'Brien *et al*. [7], who found significant differences in TNF-alpha level in the PwS group of 13.49 pg/ml ± 0.42 and 6.79 pg/ml ± 0.42 in the control group. However, different results which found lower TNF-alpha level in the PwS group was also reported by Tian *et al*. [8], Lv *et al*. [9], and Zhu *et al*. [10].

Previous studies showed inconsistent results regarding the TNF-alpha level in PwS, some of them reported an increase and others reported a decrease in TNF-alpha level. To the best of the authors' knowledge regarding the current studies that discuss this issue, there have been no studies that assessed TNF-alpha level on PwS with a specific race, and it encouraged the authors to do this study measured the Malayan-Mongoloid Race in Medan, Indonesia. The results were expected to provide an overview of TNF-alpha level in PwS of Malayan-Mongoloid race and its correlation with positive and negative symptoms in schizophrenia.

## Methods

This study was a cross-sectional analytic study, which compared two groups, namely the PwS group and the control group. Subjects were collected for 3 months at the Mental Hospital of Provinsi Sumatra Utara, which was a referral hospital for people with a mental health condition in the province. Inclusion criteria for PwS were: Malayan-Mongoloid race, schizophrenic patients, diagnosed according to the 10th edition of the International Classification of Disease and Related Health Problems criteria, aged 15–40 years, cooperative and willing to be interviewed. The exclusion criteria were: Having a history of previous mental disorders and a general medical condition that affects brain structure, obesity. Meanwhile, the inclusion criteria of the control group were: Malayan-Mongoloid race, age 15–40 years, cooperative and willing to be interviewed, and did not have a family history of mental disorders. Exclusion criteria for the control group were: Having a history of previous mental disorders and a general medical condition that affected brain structure, obesity.

The sample size calculation used the following formula: In this study, the sample size was 51 PwS and 52 controls. The research sample was obtained using non-probability sampling with a consecutive sampling type. Furthermore, the explanation was given to the subjects and their family relations, while in the control group, the explanation was given directly to the subjects, and directly signed the consent letter after they already understood the purpose of this study. Before the blood was drawn, the subjects were asked to fast for 8–10 h. Blood plasma sampling was carried out as follows: the subject would undergo a blood test, which was taken with a sterile syringe from a 6 ml median cubital vein at 7-9 a.m. The blood was put into a vacutainer containing ethylenediaminetetraacetic acid and stored at 4–8°C until plasma was obtained. The ELISA examination was then performed using the Quantikine Human TNF-alpha kit from R&D system and read the results using the ThermoFisher machine.

## Results and Discussions

The results of this study were divided into three subsections, namely baseline comparison between groups, comparison of TNF-Alpha level between PwS and control groups, and TNF-Alpha level in PwS with the Malayan-Mongoloid Race.

### *Baseline comparison between groups*

Based on Table 1, it was found that most of the subjects of the PwS group were men, they were 39 (76.5%), with an average age of 36 (28.00–40.00) years, and a positive and negative syndrome scale score of 96.00 (81.00–110.00). The results of this study found that there were more PwS subjects with male sex, 39 of the total 51 PwS subjects (76.5%) it was the same as those reported by Lv *et al*. [9] 72 people (80.89%, n = 89), Tian *et al*. [8] and Naudin *et al*. [3]. Li *et al*. [11] concluded why the male of PwS was hospitalized more than female of PwS, and it was because female of PwS was <50% experienced inpatient care and more responsive to treatment. Some other possibilities that cause the number of PwS male more often hospitalized compared to PwS female were because the male of PwS was less adherent to treatment, the ratio of the number of PwS male more than PwS female, and often commit suicide so that more often hospitalized [12].

**Table 1: Baseline comparison between groups**

| Variables | Group | |
|---|---|---|
| | Schizophrenia (n=51) | Control (n=52) |
| Sex | | |
| Male | 39 (76.5%) | 28 (53.8%) |
| Female | 12 (23.5%) | 24 (46.2%) |
| Age | 36.00 (28.00-40.00) | 29.00 (18.00-40.00) |
| PANSS Score | 96.00 (81.00–110.00) | |

### *Correlation of TNF-alpha level with PANSS scores in the schizophrenia group*

Table 2 showed that in the schizophrenia group, statistically, there was no significant correlation between TNF-alpha level and PANSS score (p = 0.594), the correlation was very weak, but it had a positive correlation means that the higher TNF-alpha level was, the higher PANSS score would be. Ergün *et al*. also reported the lack of correlation between TNF-alpha and PANSS score, [13], with a negative correlation direction. Kubistova *et al*. [14], Ajami *et al*. [15], and Luo *et al*. [16] reported similar results, who found that there was no TNF-alpha correlation with PANSS score on PwS. However, a different result from those studies was reported by Turhan *et al*. [17], who found the level of TNF-alpha serum had significant correlation, weak correlation, and negative correlation directions.

**Table 2: Correlation test result between the tumor necrosis factor-alpha level and the PANSS score in the schizophrenia group**

| Group | PANSS score | | |
|---|---|---|---|
| | n | r | p-value |
| Schizophrenia | | | |
| Tumor necrosis factor-alpha level | 51 | 0,076 | 0,594 |

Spearman correlation test.

Thus far, it is still unclear how cytokines can affect clinical symptoms in PwS [16]. One theory states that TNF-alpha, which is one of the proinflammatory cytokines, also experiences an increase in Th1 and Th17 activation, which in turn activates the hypothalamic-pituitary-adrenal axis and subsequently activates the secretion of serotonin neurotransmitters or releases neurotoxic glutamic acid [15]. The positive correlation between TNF-alpha and PANSS score in this study could indicate that if there is an increase in TNF-alpha, there has been an acceleration of the neuro

progressive process, which could eventually worsen the symptoms of PwS [17]. We have provided Figure 1 to show the scatter graph of the correlation analysis.

### *Comparison of TNF-alpha level between the schizophrenia and control groups of the Malayan-Mongoloid race*

Mann–Whitney test result in Table 3 shows that the variable of TNF-alpha level showed a value of $p < 0.001$, which means that there was a significant difference in TNF-alpha level between the schizophrenia group and the control group.

**Table 3: Results of comparative analysis of tumor necrosis factor-alpha level between the schizophrenia and the control group**

| Variable | Group | | |
|---|---|---|---|
| | Schizophrenia (n=51) | Control (n=52) | p value |
| TNF-alpha level[a] | 3.17 (0.60-43.80) | 16.40 (5.18-56.10) | <0.001 |

[a]Mann–Whitney test.

In this study, the mean of TNF-alpha levels in the PwS group was lower at 3.17 (0.60–43.80) pg/dl, compared to the control group at 16.40 (5.18–56.10) pg/dl. There were several similar results of the studies which found the lower TNF-alpha level in the PwS group compared to the control group, they were the studies conducted by Tian *et al*. [8], who reported TNF-alpha level in the PwS group (9.5 ± 2.1 pg/dl) compared to the control group (10.7 ± 1.8 pg/dl). Then, Lv *et al*. [9] found TNF-alpha level in the PwS group (10.1 ± 2.0 pg/dl) and control group (37.8 ± 3.4 pg/dl), and Zhu *et al*. [10] who obtained the TNF-alpha value in the PwS group (8.2 ± 2.0 pg/dl) and the control group (28.1 ± 13.3 pg/dl). Meanwhile, the other studies show different results that TNF-alpha levels were higher in the PwS group compared to the control group reported by Naudin *et al*. [3] and Simamora *et al*. [18]. Some conditions that are thought to affect lower TNF-alpha levels are the chronicity of schizophrenia and antipsychotic drugs consumed by PwS [9]. Low levels of inflammatory cytokines in the brain can still affect complex brain functions such as nerve activity, memory, mood, anxiety, and cognition [19], [20]. Cytokines are thought to be involved in regulating the work of several neurotransmitters such as dopamine, serotonin, noradrenaline, and glutamate [21]. All of these neurotransmitters have more or less influence in the etiology of schizophrenia, specifically dopamine. In this case, TNF-alpha plays an important role in regulating multiple events, including immunity and inflammation. It can be concluded that the decrease in TNF-alpha level in the PwS group indicates that there has been a defect during the induction of inflammatory pathways or active inhibition of the cytokines [9].

This research is the first study in Indonesia which was specializing on PwS of Malayan-Mongoloid Race, and there were no previous studies which focused on PwS in certain races. Reports from Ferguson

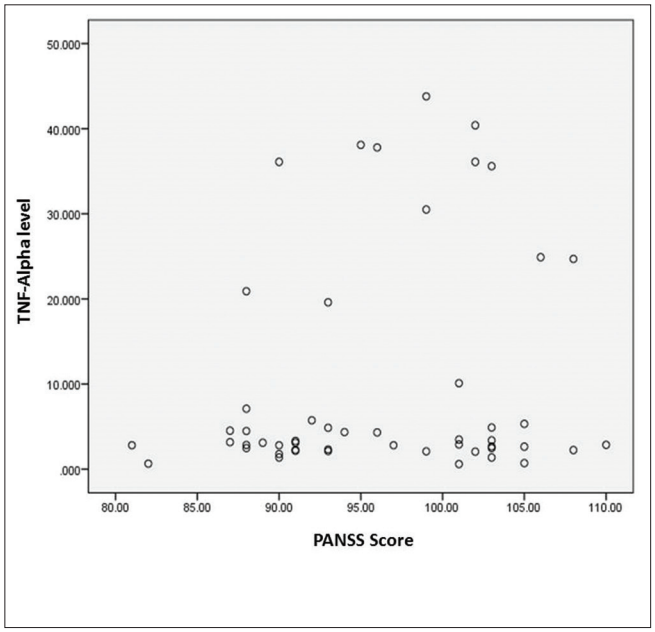


*Figure 1: Scatter graph correlation analysis results between the tumor necrosis factor-alpha level and PANSS score*

*et al*. [22], African-American Race can have higher cytokine levels compared to the Caucasian Race. Other studies also find the tendency of African-American Race to have higher cytokine level [23], [24]. The same tendency as the African-American Race was also found in the Asian Race [25]. Meanwhile, a study conducted by Liu *et al*. [26] found that Han race in China tended to have certain diseases if they had a TNF-alpha polymorphism and one study that found cytokine level could be more elevated in Caucasoid Race compared to African-American Race for the response of certain vaccines [27]. In this case, it can be concluded that race is also one of the factors toward differences in cytokine levels of each person. Figure 2 is provided to show the boxplot graph of Mann-Whitney test.

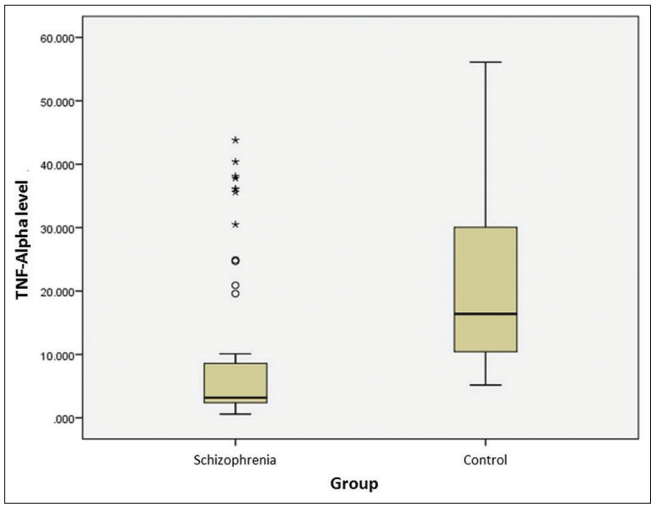


*Figure 2: Boxplot graph result of the comparison analysis of tumor necrosis factor-alpha level between the schizophrenia group and the control group*

## Conclusions

One of the factors that were thought to have an essential role in the development of schizophrenia was the inflammatory process that had begun since PwS was in the womb. The existing of cytokines affected the development of nerves, then after the PwS adult started interacting with the environment, the existence of genes in his body triggered the occurrence of schizophrenia. This study found that there was no correlation between TNF-alpha and the severity of the symptoms of schizophrenia obtained based on the PANSS score, yet it had a positive correlation direction. Thus, it can be concluded that the higher levels of TNF-alpha would impact on the severity symptoms experienced by PwS. The difference of TNF-alpha levels found in the PwS and control groups was that the lower TNF-alpha level in the schizophrenia group could be influenced by several things, including body mass index, race, smoking history, and other things that were not all controlled in this study. In the future, cohort studies and control of confounding factors will be more able to prove the correlation of cytokines with schizophrenia as one of the causes of the disease.

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