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*by Andi Jayalangkara*

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## The Effectiveness of Chlorpromazine to Decrease the Level of Tumor Necrosis Factor-Alpha Serum in Schizophrenic Patients with Coronavirus Disease 2019

Andi Jayalangkara Tanra<sup>1\*</sup>, Ahmad Andi Sameggu<sup>1</sup>, Rinvil Renaldi<sup>1</sup>, Burhanuddin Bahar<sup>2</sup>, Saidah Syamsuddin<sup>1</sup>, Muhammad Ilyas<sup>3</sup>, Sonny T. Lisal<sup>1</sup>

<sup>1</sup>Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia; <sup>2</sup>Department of Public Health, Faculty of Public Health, Hasanuddin University, Makassar, South Sulawesi, Indonesia; <sup>3</sup>Department of Pulmonology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

### Abstract

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**Keywords:** Schizophrenia; Chlorpromazine; Tumor necrosis factor-alpha; Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019

\*Correspondence: Andi Jayalangkara Tanra, Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. E-mail: [ajtanna@yahoo.com](mailto:ajtanna@yahoo.com)

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**BACKGROUND:** The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2. The COVID-19 pandemic has also had an impact on mental health, including those with schizophrenia (SCH). There were 131 inpatient schizophrenic patients who were confirmed positive for COVID-19 at Dadi Makassar Hospital, South Sulawesi, Indonesia, but these patients did not experience any clinical symptoms of COVID-19. Chlorpromazine as an antipsychotic also has antiviral and anti-inflammatory effects in schizophrenic patients with COVID-19, and the schizophrenic neuroinflammation is very likely to occur in patients with COVID-19 infection.

**AIM:** The researchers tried to examine the effectiveness of chlorpromazine on serum TNF- $\alpha$  values in schizophrenic patients with COVID-19.

**METHODS:** This research is a nested case-control study. The study was conducted on schizophrenic patients with mild and asymptomatic cases of COVID-19 at Dadi Mental Hospital with a sample of 40 patients compared to 42 schizophrenic patients who were not COVID-19. Study subjects received chlorpromazine 100 mg/day for 4 weeks. Serum tumor necrosis factor-alpha (TNF- $\alpha$ ) concentration were measured by enzyme-linked immunosorbent assays when COVID-19 was first confirmed and after 4 weeks. Positive and negative syndrome scale (PANSS) and clinical global impression SCH (CGI-SCH) examinations were also performed to measure the clinical symptoms of SCH.

**RESULTS:** The comparison of baseline TNF-serum levels that increased in the schizophrenic group with COVID-19 was 9.33 pg/ml higher, compared to the schizophrenic group without COVID-19. The decrease in TNF-levels in the schizophrenic group with COVID-19 of 7.96 pg/ml ( $p < 0.001$ ) indicated an improvement in TNF-serum levels at week 4. Meanwhile, there was no significant decrease in serum TNF-levels in the non-COVID-19 schizophrenic group ( $p > 0.05$ ).

**CONCLUSION:** The serum TNF- $\alpha$  value of schizophrenic patients with COVID-19 is higher than schizophrenic patients without COVID-19. Coadministration of chlorpromazine, antipsychotics, and COVID-19 therapy reduces serum TNF- $\alpha$  values in schizophrenic patients with COVID-19. The administration of chlorpromazine and antipsychotic in therapeutic doses reduced the total PANSS and CGI-SCH values.

## Introduction

A case of pneumonia with no known cause was first reported in Wuhan, Hubei Province, China, in December 2019. The disease is spreading rapidly globally and the World Health Organization has declared the disease a coronavirus disease 2019 (COVID-19) caused by a virus. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) declared a global pandemic in March 2020 [1]. The COVID-19 pandemic has created an unprecedented crisis of infectious diseases in the world. As of March 8, 2021, globally, there have been 121 million confirmed cases of COVID-19 with 2.7 million deaths. Meanwhile, according to the Ministry of Health, it reported 1,386,566 confirmed cases of COVID-19 with 38,547 deaths so that research continues to find an effective anti-viral to treat COVID-19 so that it ends soon.

The COVID-19 pandemic has also had an impact on mental health. Psychological and behavioral symptoms that often appear in the form of anxiety, sleep disturbances, frustration, feelings of insecurity, irritability, avoiding health services for fear of being considered sick with COVID-19, and risky behaviors such as increased alcohol consumption, substance abuse, smoking, changes in work patterns, isolation, and increasing conflict in the family environment [2]. Severe mental disorders such as schizophrenia (SCH) are also affected by the COVID-19 pandemic. In a study at New York University, there were 75 patients with SCH spectrum disorder who were confirmed positive for COVID-19 and 20 of them died. This makes SCH a high-risk factor for mortality in COVID-19 patients [3]. A study at Greater Kansas City University, 55 patients with psychotic symptoms with COVID-19 in intensive care unit (ICU) received chlorpromazine at an average dose of 70.8 mg/day [4].

Based on clinical observations, as many as 80 patients with mental disorders at the Dadi Makassar Special Hospital were positive for COVID-19 in December 2020 and the majority of patients had no symptoms and some mild symptoms. According to the latest data in February 2021, there were again 51 positive COVID-19 patients who came from different wards from December 2020 case, and all patients did not experience any clinical symptoms of COVID-19. The patient received typical and atypical anti-psychotic therapy including haloperidol, chlorpromazine, risperidone, and clozapine. Appropriate intervention is needed in mental disorders with COVID-19 to prevent high mortality.

Chlorpromazine is a dimethylamine derivative of phenothiazine which is used in the treatment of both acute and chronic psychosis [5]. Chlorpromazine is believed to have potential as an anti-inflammatory which can be beneficial in COVID-19 patients [6]. In particular, *in vitro* studies [7], [8], it was found that chlorpromazine decreased the replication of the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-1 viruses which became the basis for the FDA approved chlorpromazine as a MERS-CoV therapy. The anti-viral mechanism may be through the dynamin inhibitor clathrin-mediated endocytosis [9].

Chlorpromazine has a role in the dysregulation of pro-inflammatory agents in SCH, in accordance with the theory of neuroinflammation in SCH. Pro-inflammatory agents involved in SCH include interleukin (IL)-1 $\beta$ , IL-2, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [10]. *In vitro* studies on mouse models [11], chlorpromazine administration was associated with decreasing pro-inflammatory cytokines IL-2, IL-4, interferon- $\alpha$ , TNF- $\alpha$ , and stimulating granulocyte macrophage colonies as well as increasing anti-inflammatory cytokine IL-10, specifically on *in vitro* studies [12]. Chlorpromazine dose of 300 mg/day, TNF- $\alpha$  was found to be more significant at concentrations multiples of 0.25 times (75 mg/day) and 2 $\times$  (600 mg/day).

Several studies have explained the association of TNF- $\alpha$  with SCH. Lee's study found an increase in serum TNF- correlation with the incidence of SCH [13]. Serum TNF-levels are also associated with the level of symptoms of SCH, increased serum TNF-levels are significantly correlated with more severe clinical symptoms of SCH [14]. However, Narla's research states that changes in brain chemistry and structure in SCH are caused by strong gene dysregulation so that not only microglia and TNF-play a role but can also respond to brain stem cells, neurons, and oligodendrocytes [15].

The neuroinflammatory process in SCH also occurs in infection. In COVID-19 infection, the virus is able to produce an exaggerated immune reaction in the host. In some cases, what is collectively called a "cytokine storm" occurs. Cytokine storm is an event

of excessive inflammatory reaction in which there is rapid and large production of cytokines in response to an infection. In relation to COVID-19, it was found that there was a delay in the secretion of cytokines and chemokines by innate immune cells due to blockade by non-structural viral proteins. Furthermore, this leads to a spike in pro-inflammatory cytokines and chemokines (IL-6, TNF-, IL-8, MCP-1, IL-1 $\beta$ , CCL2, CCL5, and interferon) through activation of macrophages and lymphocytes. The release of these cytokines triggers the activation of adaptive immune cells such as T cells, neutrophils, and NK cells, along with the continued production of pro-inflammatory cytokines. This rapid surge of pro-inflammatory cytokines triggers inflammatory infiltration by lung tissue which causes lung damage to epithelium and endothelium. This damage can lead to acute respiratory distress syndrome and multiorgan failure that can lead to death in a short time [16], [17].

Accordingly, chlorpromazine as an anti-psychotic also has anti-viral and anti-inflammatory effects in schizophrenic patients with COVID-19, and the neuroinflammation in SCH is very likely to occur in patients with COVID-19 infection [6], [18], [19]. Therefore, the researchers tried to examine the effectiveness of chlorpromazine on serum TNF-values in schizophrenic patients with COVID-19.

## Subjects and Methods

This research is a nested case-control research, conducted at the Mental Hospital "Dadi" South Sulawesi (Makassar, Indonesia). This research has received ethical approval from the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University, with Number: 341/UN4.6.4.5.31/PP36/2021. All patients and families signed informed consent forms before inclusion in the study.

Research subjects were taken by consecutive sampling. The inclusion criteria were SCH sufferers according to DSM V and diagnosed with mild-moderate and asymptomatic COVID-19 based on the results of the reverse transcription-polymerase chain reaction (RT-PCR) swab examination. A 20–50 years old, currently hospitalized, receiving chlorpromazine therapy at a dose of 100–300 mg/day and a therapeutic dose of antipsychotic at least 4 weeks before the study, can communicate verbally and have psychotic clinical symptoms with a total positive and negative syndrome scale (PANSS) score <95 (mild) and willing to participate in the research. Exclusion criteria had a history of consuming and abusing psychotropic drugs, alcohol and narcotics, taking anti-inflammatory drugs or steroids, and having severe physical illness that was

not caused or related to COVID-19. Dropout criteria if during the implementation of the study, there are side effects of treatment, the patient dies or the patient refuses to continue the study.

We recruited 80 subjects and then divided them into two groups. The first group, namely, SCH with COVID-19, consisted of 40 people receiving chlorpromazine at a dose of 100–300 mg/day, antipsychotics, COVID-19 therapy, and the second group, SCH without COVID-19, consisting of 40 people receiving chlorpromazine at a dose of 100–300 mg/day, and antipsychotics alone for 4 weeks. Psychotic clinical symptoms were measured 3 times in 4 weeks (baseline, week 2, week, and week 4) using the PANSS and clinical global impression SCH (CGI-SCH) scales. Serum TNF-levels were measured at baseline and at week 4. This study was using more than 1 antipsychotic which is risperidone at 4 mg and 6 mg doses and haloperidol at 4.5 mg, 7.5 mg, and 15 mg doses.

TNF-levels were measured in the form of serum which was duplicated by the enzyme-linked immunosorbent assay (ELISA) method from a special TNF- $\alpha$  kit. The examination was carried out at the Hasanuddin University Medical Research Center Laboratory. The examination followed the instructions according to the human TNF- $\alpha$  ELISA kit protocol with product code RAB0476 Sigma-Aldrich Millipore brand. Blood samples were taken at the beginning of the study and after 4 weeks.

PANSS is a psychometric tool to assess positive, negative symptoms and general psychopathology. PANSS consists of 33 items, each of which is rated on a 7-point scale. After assessing each item, the accumulated value will be interpreted as follows: Mild pain = 58, moderate pain = 75, visible pain = 95, severe pain = 116, and very sick = 147 [19].

CGI-SCH is a valid and reliable instrument in evaluating the severity and healing response of SCH. CGI-SCH is a simpler scale because it only consists of 25 types, namely, the severity of the disease and the degree of change. The severity of the disease evaluates the mood during the week before the evaluation, whereas the severity of the change evaluates the change of the score. Each type contains five different ratings (positive, negative, mental stress, cognitive, and global) which are evaluated using a 7-point ordinal scale [20].

Possible side effects and complications with the administration of chlorpromazine may occur during the study. So far, the administration of chlorpromazine 100 mg/day is well tolerated, and no clinical side effects have been detected. Two of the research subjects only experienced mild side effects in the form of tremors and could be controlled by administering an anticholinergic in the form of trihexyphenidyl.

## Results

### Characteristics of research subjects

This study began screening the treatment group of SCH sufferers with COVID-19 who were hospitalized at the Hasanuddin University Teaching Hospital and its network from January 2021 to May 2021. Of the 131 schizophrenic patients with COVID-19 who were screened, 42 patients were found (32.06%) met the inclusion criteria (Table 1). A total of 89 patients did not meet the inclusion criteria, namely, 24 patients aged more than 50 years, 13 patients with a total PANSS value >96, 41 patients did not receive chlorpromazine 100–300 mg/day, seven patients had not been hospitalized for 3 months, and four patients taking anti-inflammatory due to skin disease. Among the 42 patients in the treatment group, only 40 patients completed until week 4 because two study subjects dropped out because they could be outpatients. Then, screening was carried out for the schizophrenic group without COVID-19 by adjusting the characteristics of the schizophrenic group with COVID-19 to obtain homogeneity and obtained 40 patients in the control group.

**Table 1: Characteristics of research subjects (n=40)**

Variable	Schizophrenia with COVID-19 n = 40	Schizophrenia is not COVID-19 n = 40	p
Mean $\pm$ SD)	40.93 $\pm$ 7.55	40.25 $\pm$ 8.10	0.806
Gender (%)			
Male	38 (47.5)	38 (47.5)	1.000
Female	2 (2.5)	2 (2.5)	
Education (%)			
No school	10 (12.5)	11 (13.8)	0.697
Elementary school	16 (20.0)	17 (21.2)	
Junior high school	4 (5.0)	1 (1.2)	
Senior high school	9 (11.2)	9 (11.2)	
Undergraduate	2 (2.5)	1 (1.2)	
Job (%)			
Does not work	23 (28.8)	23 (28.8)	0.786
Farmer	13 (16.2)	10 (12.5)	
Private sector employee	1 (1.2)	2 (2.5)	
Trader	1 (1.2)	3 (3.8)	
Housewife	2 (2.5)	2 (2.5)	
Antipsychotic per day (%)			
Risperidone 4 mg	15 (18.8)	24 (28.8)	0.023*
Risperidone 6 mg	2 (2.5)	0 (0.0)	
Haloperidol 4.5 mg	4 (5.0)	5 (6.2)	
Haloperidol 7.5 mg	10 (12.5)	1 (7.5)	
Haloperidol 15 mg	9 (11.2)	11 (13.8)	
Equivalent dose of antipsychotic	512 $\pm$ 217.26	522.5 $\pm$ 239.48	0.371
(Mean $\pm$ SD)			
Length of treatment (Mean $\pm$ SD)	160.5 $\pm$ 139.82	153.25 $\pm$ 132.75	0.875

\*Significant P < 0.05. Paired t-test and Mann-Whitney U-test, COVID-19: Coronavirus disease 2019.

There were no significant differences in age, gender, education, occupation, sedative antipsychotic dose, antipsychotic equivalent dose, and length of stay SCH with COVID-19 and SCH without COVID-19 group ( $p > 0.05$ ).

There was no significant difference in serum TNF-values with the level of clinical symptoms of COVID-19 ( $p > 0.05$ ). COVID-19 therapy received in the schizophrenic group with asymptomatic COVID-19 (33 patients) received azithromycin, oseltamivir, Vitamin C, and Vitamin D, but patients with mild symptoms (five patients) and moderate symptoms (two patients) received additional therapy with N-acetylcysteine (Table 2).

**Table 2: Comparison of serum TNF-values with the level of clinical symptoms of COVID-19**

COVID-19 clinical symptoms level	n (%)	TNF- $\alpha$ baseline	p	TNF- $\alpha$ 4 <sup>th</sup> week	p
		Mean $\pm$ SD		Mean $\pm$ SD	
Asymptomatic	33 (82.5)	25.07 $\pm$ 3.13	0.530	17.33 $\pm$ 4.79	0.706
Mild symptoms	5 (13)	26.16 $\pm$ 2.98		16.62 $\pm$ 3.76	
Moderate symptoms	2 (5)	33.35 $\pm$ 7.13		19.81 $\pm$ 10.13	

\*Significant  $P < 0.05$  (Kruskal-Wallis test), COVID-19: Coronavirus disease 2019, TNF: Tumor necrosis factor.

Based on Table 3, it was found the results of routine hematology and blood chemistry examinations in the normal treatment group except for lymphocytopenia and neutropenia, and 34 study subjects (85%) had bilateral pneumonia and 4 subjects (10%) with unilateral pneumonia on computed tomography (CT) thorax examination results (Figure 1).

**Table 3: Supporting examination results for the schizophrenic group with COVID-19**

Hematology	Mean $\pm$ SD	Units	Referral value
51. Hematocrit results			
WBC	7.44 $\pm$ 1.93	10 <sup>9</sup> /L	3.17–8.40
RBC	4.59 $\pm$ 0.65	10 <sup>12</sup> /L	3.72–5.70
HB	12.85 $\pm$ 1.86	g/dL	11.0–16.6
HCT	38.01 $\pm$ 5.34	%	35.2–52.1
MCV	82.81 $\pm$ 6.41	fL	86.1–102.4
MCH	28.17 $\pm$ 2.6	pg	26.8–32.4
MCHC	34.09 $\pm$ 1.2	g/dL	29.6–33.2
PLT	276.63 $\pm$ 64.06	10 <sup>9</sup> /L	167–390
Neut	9.58 $\pm$ 15.37	%	50–70
Lymph	6.59 $\pm$ 11.84	%	20–40
Mono	1.75 $\pm$ 2.79	%	2–8
Eos	1.43 $\pm$ 2.56	%	0.02–0.05
Baso	0.07 $\pm$ 0.12	%	0–0.06
GDS	114.38 $\pm$ 28.10	mg/dl	110–200
Urea	28.52 $\pm$ 4.50	mg/dl	8.0–48.0
Creatinine	0.79 $\pm$ 0.18	mg/dl	0.6–1.2
SGOT	37.62 $\pm$ 56.64	U/l	9–40
SGPT	30.44 $\pm$ 41.28	U/l	7–55
NLR	1.89 $\pm$ 0.98		
CT thorax results	n (%)		
Normal	2 (5.0)		
Bilateral pneumonia	33 (82.5)		
Unilateral pneumonia	4 (10.0)		
Bilateral pneumonia+Effusion	1 (2.5)		

WBC: White blood cell, RBC: Red blood cell, HB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet, COVID-19: Coronavirus disease 2019, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, NLR: Neutrophil-to-lymphocyte ratio, CT: Computed tomography.

### Comparison of serum TNF- $\alpha$ levels

A total of 80 study subjects who received chlorpromazine 100–300 mg/day were measured for serum TNF-levels at the beginning of confirmed COVID-19 (baseline) and at week 4. The measurement results are shown in Table 4.

**Table 4: Comparison of serum TNF-levels in the schizophrenic group with COVID-19 and the schizophrenic group without COVID-19**

TNF- $\alpha$ serum	Schizophrenia with COVID-19+ chlorpromazine n = 40	Schizophrenia not COVID-19+ chlorpromazine n = 40	Control n = 10
	(pg/ml)	(pg/ml)	(pg/ml)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Baseline	25.32 $\pm$ 3.26	15.99 $\pm$ 2.65	13.67 $\pm$ 1.47
	p	p	
4 <sup>th</sup> week	17.36 $\pm$ 4.83	15.59 $\pm$ 3.33	

\*Significant  $P < 0.05$  (paired t-test), COVID-19: Coronavirus disease 2019, TNF: Tumor necrosis factor.

The comparison of baseline TNF-serum levels that increased in the schizophrenic group with

COVID-19 was 9.33 pg/ml higher, compared to the schizophrenic group without COVID-19. The decrease in TNF-levels in the schizophrenic group with COVID-19 of 7.96 pg/ml ( $p < 0.001$ ) indicated an improvement in TNF-serum levels at week 4. Meanwhile, there was no significant decrease in serum TNF-levels in the non-COVID-19 schizophrenic group ( $p > 0.05$ ) (Figure 2).

### Total PANSS value comparison

Comparison of Total PANSS values in the SCH with COVID-19 group and the SCH non-COVID-19 group measured in the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week is shown in Table 5.

**Table 5: Comparison of total PANSS values against the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week in the schizophrenic group with COVID-19 and the schizophrenic group without COVID-19**

Treatment	Schizophrenia with COVID-19 n = 40	p	Schizophrenia is not COVID-19 n = 40	p
	Mean $\pm$ SD		Mean $\pm$ SD	
PANSS early week	75.10 $\pm$ 10.54	<0.001*	73.70 $\pm$ 3.65	<0.001*
PANSS week 2	73.13 $\pm$ 10.55		71.70 $\pm$ 3.62	
PANSS week 4	69.18 $\pm$ 10.36		69.75 $\pm$ 8.84	

\*Significant  $P < 0.05$  (Friedman test), COVID-19: Coronavirus disease 2019, PANSS: Positive and negative syndrome scale.

Based on the bivariate analysis using the Friedman test, in the schizophrenic group with COVID-19, the total PANSS value compared between the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week showed a significant difference ( $p < 0.05$ ). There is a decrease in the PANSS value which describes the improvement in clinical symptoms of schizophrenic patients after receiving therapeutic doses of antipsychotics and 100 mg chlorpromazine.

In the non-COVID-19 schizophrenic group, the total PANSS value compared between the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week showed a significant difference ( $p < 0.05$ ). There is a decrease in the PANSS value which describes the improvement in clinical symptoms of schizophrenic patients after receiving therapeutic doses of antipsychotics and 100 mg chlorpromazine (Figure 3).

### CGI-SCH value comparison

Comparison of CGI-SCH values in the schizophrenic group with COVID-19 and the schizophrenic group without COVID-19 measured in the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week as shown in Table 6.

**Table 6: Comparison of CGI-SCH values in the schizophrenic group with COVID-19 and the schizophrenic group without COVID-19 measured in the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week**

Treatment	Schizophrenia with COVID-19 n = 40	p	Schizophrenia is not COVID-19 n = 40	p
	Mean $\pm$ SD		Mean $\pm$ SD	
CGI-SCH early week	21.03 $\pm$ 2.97	<0.001*	20.68 $\pm$ 1.09	<0.001*
CGI-SCH week 2	20.40 $\pm$ 2.96		20.03 $\pm$ 1.12	
CGI-SCH week 4	19.35 $\pm$ 2.79		19.43 $\pm$ 1.08	

\*Significant  $P < 0.05$  (Friedman test), CGI-SCH: Clinical global impression schizophrenia, COVID-19: Coronavirus disease 2019.

Based on bivariate analysis using the Friedman test, in the schizophrenic group with COVID-19, the CGI-SCH values were compared between the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week showing a significant difference ( $p < 0.05$ ). There is a decrease in the CGI-SCH value which describes the improvement in severity and healing response in schizophrenic patients with SCH after receiving therapeutic doses of antipsychotics and chlorpromazine 100 mg (Figure 4).

In the non-COVID-19 schizophrenic group, the CGI-SCH values compared between the initial week, 2<sup>nd</sup> week, and 4<sup>th</sup> week showed a significant difference ( $p < 0.05$ ). There is a decrease in the CGI-SCH value which describes the improvement in severity and healing response in schizophrenic patients with SCH after receiving therapeutic doses of antipsychotics and chlorpromazine 100 mg.

## Discussion

This study was conducted to test the effectiveness of chlorpromazine on serum TNF-levels in schizophrenic patients with COVID-19 as well as total PANSS and CGI-SCH values for 4 weeks. The basic characteristics of the research subjects including age, sex, education, occupation, equivalent dose of antipsychotic, and length of hospitalization were not found to be significantly different between the treatment group and the control group ( $p > 0.05$ ). However, there was a significant difference between the treatment group and the control group ( $p = 0.023$ ). Thus, the research subjects are quite homogeneous.

The mean age of the research subjects was  $40.93 \pm 7.55$  in the treatment group and  $40.25 \pm 8.10$  in the control group with more males than females. According to the theory, the prevalence of SCH in men and women is the same. However, there are differences in the onset and course of the disease. Earlier onset was found in the male sex. Where more than half of people with SCH are men, but only a third are women and were first treated before the age of 25 years. Peak age of onset is 10–25 years for men and 25–35 years for women [21].

There are several hypotheses that can explain the sex differences in SCH. The theory of SCH involves gonadal hormones, such as estrogen, which play a neuroprotective role preventing the pathology of SCH in women. Estrogen deficiency at menopause is strongly associated with the severity of psychiatric symptoms in women. A negative correlation between patients' plasma estrogen levels and symptoms of SCH was also reported in men. Recent research has shown that sex chromosomes, XX or XY, can play a role in neurodevelopment in the form of a short arm proximal to the X chromosome, which is often found in people

with SCH. Gender-specific associations of certain dopaminergic genes (catechol-O-methyltransferase and monoamine oxidase) are also associated with SCH. Meanwhile, dopamine deficits and excesses have been associated with positive and negative SCH symptoms in general [22].

Most of the last education level of people with SCH in this study was elementary school and did not finish elementary school. Children and adolescents who suffer from SCH have academic and mathematics achievement that is much worse than individuals who are not schizophrenic. Individuals with SCH are also less likely to have higher education than individuals without SCH. In addition, adolescents are considered at risk for SCH because they have a history of premorbid psychotic-like experiences or have family members with severe mental disorders. Poor academic performance before age 16 associated with the appearance of prodromal symptoms may represent a premorbid cognitive marker that is susceptible to SCH later in life [23].

In this study, 57.6% of the research subjects did not work. There are several criteria of job function that need to be considered in people with SCH, namely, the work is paid or not, part time or full time. Most people with SCH often work without pay at home. However, 10–20% of people with SCH can also work competitively, where the job requires a normal recruitment process and is not part of a job program created by a social company such as job training for people with mental disorders. People with SCH who are employed in normal jobs, generally get laid off because the company is dissatisfied with the results of the work they do [24].

The administration of antipsychotic therapeutic doses in this study was dominantly using haloperidol 4.5–15 mg/day (57.5%) in the schizophrenic group with COVID-19, while risperidone 4–6 mg/day (60%) in the schizophrenic group without COVID-19. The use of haloperidol and risperidone is an antipsychotic therapy option used in inpatients at the Dadi Regional Special Hospital, South Sulawesi Province. The typical antipsychotic haloperidol having a strong affinity for the D2 receptor was suggested as a potential effective treatment for COVID-19 based on *in vitro* assays through the Sigma 1 and Sigma 2 receptors. Molecules targeting the Sigma receptor can reduce viral infectivity through different mechanisms, including remodeling, lipids, and endoplasmic reticulum stress response [25].

However, a study by Hoertel *et al.* at Greater Paris University Hospitals examining the association of haloperidol use with intubated patients with COVID-19 concluded that there was no significant relationship between daily haloperidol dose and duration of exposure in the haloperidol exposed group of patients [26]. This research is the basis that the administration of haloperidol has no effect on the symptoms of COVID-19.

Equivalent dose ratio of antipsychotic therapy obtained in the treatment group was  $512 \pm 217.26$  and in the control group was  $522.5 \pm 239.48$ . The calculation of this equivalent dose ratio is based on the International Consensus on Antipsychotic Doses using chlorpromazine as a comparison. Haloperidol 1 mg has a chlorpromazine ratio of 60 mg, while risperidone 1 mg has a chlorpromazine ratio of 100 mg [27] so that in the treatment group, the average equivalent of haloperidol was 8.5 mg/day and the control group was equivalent to an average of 5.2 mg/day risperidone. This range [73] responds to therapeutic doses of haloperidol 5–10 mg/day and risperidone 4–6 mg/day.

Demographic characteristics also affect TNF- $\alpha$  levels. Gender has an influence on TNF-levels in psychiatric patients, female serum TNF-levels are higher in men. The mean body mass index and smoking frequency also increased TNF- $\alpha$  levels. A history of antipsychotic treatment also gave a decrease in TNF-levels in 4 weeks compared to patients not taking antipsychotics. History of comorbid disease is the most frequent confounding factor in assessing pro-inflammatory cytokines. A diagnosis of depression has higher serum TNF-levels than a diagnosis of SCH [28]. In research subjects during hospitalization, it is difficult to get access to smoking because it is prohibited while in hospital.

This study found 131 schizophrenic patients with COVID-19 who were hospitalized from [95] January 2021 to May 2021. Psychiatric inpatients have a high risk of exposure to COVID-19 because patients live in adjacent [37] rooms, are free to interact with other patients, and use shared bathrooms [29]. In addition, patients have difficulty maintaining health protocols [37] such as social distancing and hand washing due to cognitive deficits, disorganized thinking, behavioral dysregulation, and poor insight. To minimize the risk of inpatients having direct contact with visitors, restrictions are placed on family members, health workers, and field practice students [30].

Previous studies have examined the prevalence of mental disorders sufferers who are sick with COVID-19 abroad. In a study at New York University, there were 75 patients with SCH spectrum disorder who were confirmed positive for [24] COVID-19 and 20 of them died. This makes SCH a high-risk factor for mortality in COVID-19 patients [3]. A study in France with a period of February–June 2020 of 50,750 COVID-19 patients treated in the ICU, there were 823 SCH sufferers (1.6%). It was also found in the same study that age <55 years had a higher risk of being admitted to the ICU [31].

A study in Korea with a period from January to May 2020 found 128 (9.7%) of 1320 people with [9] mental disorders who were sick with COVID-19. Patients with severe mental illness had a slightly higher risk of clinically severe COVID-19 than patients without a history of mental disorders. Doctors treating patients

with COVID-19 should be aware of the risks associated with pre-existing mental illness [32].

The study with the largest population was conducted in the USA with 61.7 million adults in the electronic health database, found 1.3 million [48] (1%) people with mental disorders. There were 5450 patients with mental disorders with COVID-19 and [48] 0 people with SCH (0.8%). It was also found that people with mental disorders with COVID-19 infection [45] had an 8.5% increased risk of death compared to 5.7% for all COVID-19 patients and 4.7% for COVID-19 patients without mental disorders [33].

Patients [44] with severe mental disorders and comorbidities have a higher risk for more severe [35] COVID-19 disease. Hence, it is important to conduct personalized COVID-19 clinical management and health-care strategies before, during, and after hospitalization to reduce health disparities in the severe mental disorder population.

This study evaluates routine hematological examinations and blood chemistry of a group of SCH sufferers with COVID-19 without symptoms and mild symptoms. All 40 study subjects in the treatment group have normal results on all routine blood examinations [61] (hemoglobin, neutrophil-lymphocyte ratio, blood urea nitrogen, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, urea, and creatine), but they have neutropenia and lymphocytopenia. Several retrospective studies assessed the [12] parameters of routine hematological examination in asymptomatic and mildly symptomatic COVID-19 patients. The study in Wuhan, China, on 74 asymptomatic COVID-19 patients, the majority of the results were normal in WBC, Hb, and platelets, but found lymphocytopenia and neutropenia [34].

Decreased lymphocyte levels were reported in 20 of 29 COVID-19 patients [35]. Another study with 138 COVID-19 patients had the same lymphocytopenia as SARS-CoV and MERS-CoV [36]. A study with 41 COVID-19 patients, 63 patients experienced lympho[28]cytopenia [37]. Several hematological changes were reported in COVID-19 patients, including leukocytosis, decreased lymphocyte values, increased D-Dimer levels, neutrophilia, thrombocytopenia, eosinopenia, and basopenia. Moreover, patients with moderate-to-severe symptoms have more prominent hematological abnormalities than patients with mild and asymptomatic symptoms [38].

Lymphopenia is [86] characteristically abnormal hematologically found in SARS-CoV and MERS-CoV infections and is associa[18]ted with disease severity. These findings suggest that lymphopenia can be considered as a surrogate biomarker [18] of the adaptive immune response to SARS-CoV-2. The biological reasons associated with lymphopenia are still under investigation and may be due to dysregulation of the cytokine system [39].

Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio are both parameters that can be calculated quickly from routine blood tests. An increase in NLR 3.13 leads to a poor prognosis. The NLR describes the balance of the body's innate (neutrophil) and adaptive (lymphocyte) immune responses. In this study, it was found that the NLR was  $1.89 \pm 0.98$ , so it was sufficient to self-isolate. If asymptomatic patients are not properly identified and quarantined, they can become a source of infection and cause disease transmission. Thus, self-isolation is recommended for asymptomatic patients.

This study also evaluated CT thoracic examination, found that 34 study subjects (85%) had bilateral pneumonia and 4 subjects (10%) had unilateral pneumonia. Several studies have also reported that asymptomatic and mildly symptomatic COVID-19 patients still have abnormal CT thoracic. The study in Wuhan, China, found 52 patients (20.6%) of unilateral pneumonia and 119 (47.2%) of bilateral pneumonia [34].

Another study in Wuhan, 36 asymptomatic patients found pneumonia on CT thorax [40]. In a study in Chongqing China, 42 patients (68.9%) were asymptomatic and had mild symptoms with CT thoracic abnormalities [38]. A total of 178 patients with mild symptoms of COVID-19 have the main symptom experienced was cough [34]. The same thing was experienced by patients who were research subjects who experienced mild symptoms. The study found that patients were more likely to be asymptomatic if they met one or more of the following criteria: Young age, unilateral pneumonia, and achieved virus-free status within 5 days [34]. In a study in Jinan China, 11 asymptomatic patients with young age were detected with abnormal CT thorax results, and statistically, there was no significant difference compared to the moderately severe symptomatic group [41].

A total of 80 study subjects who received chlorpromazine 100–300 mg/day were measured for serum TNF-levels at the beginning of confirmed COVID-19 (baseline) and at week 4. Serum TNF- $\alpha$  level is a biomarker used in this study. It was found that baseline serum TNF-levels were increased in the schizophrenic group with COVID-19, compared to the schizophrenic group without COVID-19. The decrease in TNF- levels in the schizophrenic group with COVID-19 ( $p < 0.001$ ) indicated an improvement in serum TNF- levels at week 4. Meanwhile, there was no significant decrease in serum TNF- levels in the schizophrenic group without COVID-19 ( $p > 0.05$ ).

In the non-COVID-19 schizophrenic group, the average baseline serum level was  $15.99 \pm 2.65$  pg/ml, and in the 4<sup>th</sup> week, it was  $15.59 \pm 3.33$  pg/ml. Biomarkers of TNF- levels in SCH describe the process of neuron-microglia interactions in the pathophysiology of

SCH [42]. Several studies have found different levels of TNF-in schizophrenic patients. This is due to different reagents, different blood sampling times, and different research subjects. The study by Naudin obtained an average TNF- of 34 pg/ml and increased in patients with chronic SCH [43].

A study by Kim in Korea found an average TNF- of 870.82 pg/ml in schizophrenic patients and 577.51 pg/ml in normal controls, and schizophrenic patients after hospitalization and then reexamined when they returned home, TNF- $\alpha$  levels decreased to an average 850.97 pg/ml [44]. An increased inflammatory response is implicated the pathophysiology of SCH, and antipsychotic drugs may be involved in the treatment of SCH. It is also possible that some antipsychotics have anti-inflammatory activity as it was found in Kim's study that the pro-inflammatory cytokines IL-6 and TNF- $\alpha$  were significantly reduced after 6 weeks of treatment with antipsychotics [44].

A study by Luo *et al.* at Guangzhou Hospital examined changes in serum TNF-, IL-18, and IL-6 in 68 chronic schizophrenic patients at the beginning of hospitalization and at discharge, found a significant decrease in TNF- levels from 12.15 pg/ml to 11.30 pg/ml. Meanwhile, in normal control people, TNF- levels were 2.24 pg/ml [45]. This study is closest to the results of the research conducted.

The latest study by Mesa in Spain on 60 COVID-19 patients found 29 ARDS patients with a mean TNF- level of 20.89 pg/ml and 31 non-ARDS patients with an average TNF- level of 8.58 pg/ml. TNF- values were also significantly increased in ARDS compared with non-ARDS patients a week after admission, indicating the presence of high systemic inflammation. This study also found that the TNF- biomarker had a sensitivity of 48.3% and a specificity of 73.3%. Determining TNF- levels together with IL-6 can be considered as an important tool for classifying high-risk patients and planning therapy [46]. These data on TNF- levels as a comparison were due to the lack of publication of TNF- $\alpha$  levels in schizophrenic patients with COVID-19 who received antipsychotics, especially chlorpromazine.

The study by Himmerich investigated the effect of several antipsychotics on pro-inflammatory cytokines *in vitro* with chlorpromazine at a dose of 75 mg/day TNF- levels 1.82 pg/ml, a dose of 150 mg/day TNF- levels 1.56 pg/ml, a dose of 300 mg/day 1.77 pg/ml, and 600 mg/day 1.71 pg/ml [12]. So that TNF- levels reached peak levels after administration of chlorpromazine 75 mg/day and decreased TNF- levels with increasing doses of chlorpromazine.

The results showed the decrease in TNF- levels in the schizophrenic group with COVID-19 with an average of  $7.95 \pm 2.28$  pg/ml. This is in accordance with the study in Medan, in Schizophrenic patients,

the decrease in TNF- levels averaged 3.40 pg/ml [47]. Decreased levels of TNF- provide scientific evidence for antipsychotics chlorpromazine reduces serum levels of the pro-inflammatory cytokine TNF- as well as anti-viral through clathrin- and dynamin-dependent inhibitory mechanisms in SARS-CoV-2 [18], [48]. Chlorpromazine blocks the entry of the SARS-CoV-2 virus into cells by inhibiting the activation of lysosomal proteases that allow viral fusion with endosomes and the release of viral genetic material into the cytosol [18].

One of the advantages of chlorpromazine over other antivirals lies in its biodistribution. In animal experiments that after a single injection of chlorpromazine, the highest concentrations of the molecule and its metabolites were detected in the lungs, with doses of chlorpromazine 20–200 times higher than in the blood [6]. These results were confirmed in humans in a postmortem study of schizophrenic patients treated with chlorpromazine. Chlorpromazine is also highly concentrated in saliva, with concentrations 30–100 times higher than in human plasma. High concentrations of chlorpromazine in the salivary glands can reduce the salivary viral load and therefore reduce the transmission of SARS-CoV-2 [6].

Chlorpromazine has lipophilic properties so it can cross the blood–brain barrier and therefore can have a therapeutic or prophylactic effect on the neurological form of COVID-19. The cerebral distribution of chlorpromazine has been known for a long time and underlies its use for its antipsychotic action. *In vitro* studies, chlorpromazine was detected in brain tissue 15 min after a single intravenous injection, in different brain areas including cortex, caudate nucleus, putamen, and thalamus. In chronic administration to rats, the concentration of chlorpromazine in the brain has been found to be up to 25 times higher than in plasma [49].

Chlorpromazine, already routinely used in psychiatry, has an excellent tolerance profile. Side effects are known, including: Anticholinergic effects (sedation, dry mouth, constipation, and urinary retention), increased QT, and neuroleptic malignancy syndrome are a rare condition. Side effects of orthostatic and neurologic hypotension such as parkinsonism, tremor, akathisia, and dystonia are well managed with dose reduction or drug changes [50]. During this study, the only side effects that appeared were tremors and could be controlled by administering an anticholinergic in the form of trihexyphenidyl.

The critical question of what dose of chlorpromazine is required to achieve a clinically relevant anti-SARS-CoV-2 effect in humans remains unresolved because it is difficult to estimate the effective *in vivo* dose from the effective *in vitro* dose and there are no animal data in this regard. Anti-coronavirus effect of chlorpromazine. This study uses a dose of

chlorpromazine 100 mg/day and is expected to be a reference for further research regarding the appropriate dose of chlorpromazine in schizophrenic patients with COVID-19.

However, it is important to note that the decrease in serum TNF- levels in the treatment group cannot be claimed as an effect of chlorpromazine itself because the study subjects in the treatment group also received COVID-19 therapy in the form of antibiotics (azithromycin) and anti-viral (oseltamivir). Azithromycin is an antiviral and immunomodulator in the treatment of COVID-19. The use of these macrolides has been associated with improved clinical outcomes in other viral infections and CAP. Azithromycin has shown activity *in vitro* against SARS-CoV-2 and acts at several viral sites. Furthermore, azithromycin immunomodulation enhances clinical improvement in severe COVID-19, the ability to downregulate cytokine production, maintains epithelial integrity, and prevents pulmonary fibrosis. It may play a role in the hyperinflammatory stage of COVID-19 [51].

In this study, there was a combination of azithromycin and oseltamivir therapy. Lee *et al.* concluded that in hospitalized patients with influenza A pneumonia, the combination of azithromycin to oseltamivir significantly reduced pro-inflammatory cytokine synthesis, with a trend toward faster resolution of symptoms [52]. In this study, there was also a combination of azithromycin and chlorpromazine which is the same group of phenothiazines as hydroxychloroquine. In a randomized-controlled clinical trial in hospitalized patients with mild-to-moderate COVID-19, the use of hydroxychloroquine and azithromycin or hydroxychloroquine alone did not improve clinical status at 15 days compared with standard care [53]. As well as the side effects of cardiotoxicity often encountered in azithromycin combination hydroxychloroquine [51].

*In vitro* study of a combination of antiviral, antibiotics, and hydroxychloroquine therapy against SARS-CoV-2 isolated from COVID-19 patients in Surabaya. Measurements were made at several levels of cytokines. TNF- levels had no effect on azithromycin monotherapy and hydroxychloroquine monotherapy.

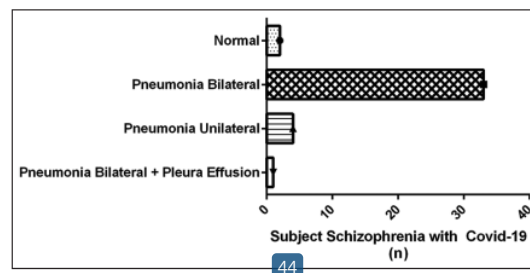


Figure 1: Results of thorax computed tomography scan of schizophrenic patients with coronavirus disease 2019

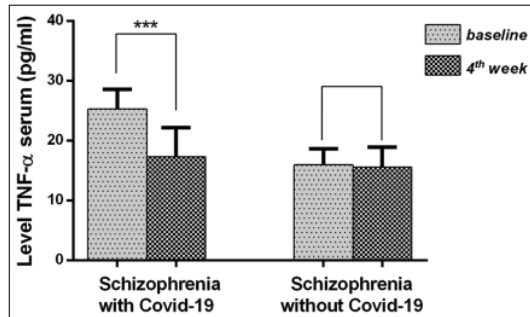


Figure 2: Comparison of serum tumor necrosis factor-levels in the schizophrenic group with coronavirus disease 2019 (COVID-19) and the schizophrenic group without COVID-19. All data are presented by mean with SD, \*\*\* $p < 0.001$  (Paired t-test)

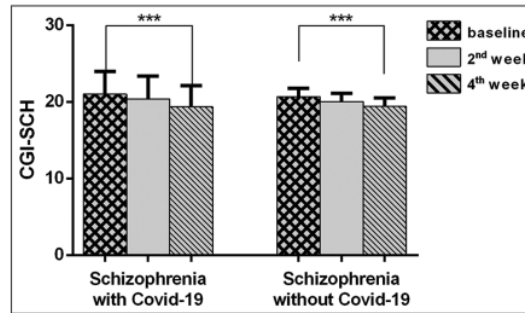


Figure 4: Comparison of clinical global impression schizophrenia values against the 1st week, 2nd week, and 4th week in the schizophrenic group with coronavirus disease 2019 (COVID-19) and schizophrenia without COVID-19. All data are presented by mean with SD. \*\*\* $p < 0.001$  (Friedman test)

However, the combination of azithromycin and hydroxychloroquine reduced TNF- levels by 25 g/mL in 24 h [54]. Hydroxychloroquine and azithromycin affect the drug's ability to inhibit or reduce the level of viral infectivity in host cells. This is predicted due to the interaction of receptors and proteins called molecular docking. This interaction can be seen from the binding site of the target macromolecule consisting of the docking algorithm stage and the scoring function so as to get the affinity value [55]. A low affinity value indicates that the conformation formed is stable, while a high affinity indicates the formation of a less stable complex. The more negative the resulting value, the stronger the affinity of the protein-ligand complex, so it is hoped that the activity will be of higher quality [56].

This supports our study which found that TNF- levels in the schizophrenic group without COVID-19 did not decrease due to chlorpromazine monotherapy, while the schizophrenic group with COVID-19 experienced a significant decrease in TNF- levels due to the combination of azithromycin as COVID-19 therapy and chlorpromazine as antipsychotic therapy.

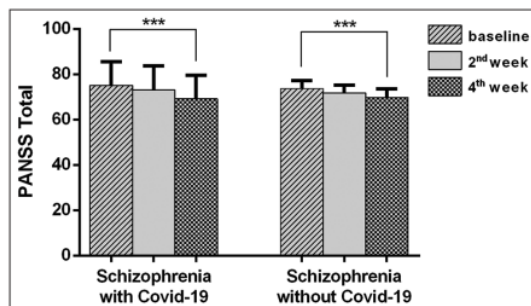


Figure 3: Comparison of total positive and negative syndrome scale scores against the initial week, 2nd week, and 4th week in the schizophrenic group with coronavirus disease 2019 (COVID-19) and the schizophrenic group without COVID-19

## Conclusion

The serum TNF- value of schizophrenic patients with COVID-19 is higher than schizophrenic patients without COVID-19. Coadministration of chlorpromazine, antipsychotics, and COVID-19 therapy reduces serum TNF- values in schizophrenic patients with COVID-19. The administration of chlorpromazine and antipsychotic in therapeutic doses reduced the total PANSS and CGI-SCH values.

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