



Differences in Interleukin-6 Levels, Neutrophil Levels, and Length of Hospitalization in Pneumonia Patients with and without Garlic Supplementation (*Allium sativum*)

Yogie Irawan, Harsini^{ID}, Yusup Subagio Sutanto^{ID}

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia

Abstract

Background: Pneumonia is an acute lung inflammation caused by various microorganisms, such as bacteria, viruses, fungi, or parasites, with high mortality and morbidity rates. The examination of IL-6 and neutrophils helps in diagnosis as a marker of inflammation, a predictor of mortality and morbidity, and is useful in evaluating the outcome of treatment. Garlic and its organosulfur content possess anti-inflammatory activity that has the potential to be used as additional therapy in pneumonia patients.

Methods: A clinical study with a pretest-posttest quasi-experimental design was conducted on pneumonia patients who were hospitalized at Dr. Moewardi General Hospital, Surakarta from August to October 2022 by consecutive sampling. The treatment group (n=20) received standard therapy plus 3.5 mg of garlic capsules per day for 6 days, while the control group (n=20) received standard therapy. Levels of IL-6 and neutrophil were calculated on the first and sixth days, while the length of hospitalization was calculated from when the patient was admitted until discharge.

Results: There was a significant IL-6 difference in the treatment group ($P=0.027$) and a neutrophil difference in the treatment group ($P=0.025$) compared to the control group, but there was no significant difference ($P=0.876$) in the length of stay in the treatment group compared to the control group.

Conclusion: Giving garlic as a supplemental therapy to pneumonia patients could significantly reduce IL-6 and neutrophil levels.

Keywords: garlic, IL-6, LOS, neutrophils, pneumonia

Corresponding Author:

Yogie Irawan | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia | michaelputra@gmail.com

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INTRODUCTION

Microorganisms such as bacteria, fungi, viruses, or parasites can cause pneumonia, an acute inflammation in the lungs, but does not include *Mycobacterium tuberculosis*. High morbidity and mortality rates are linked with pneumonia. Lower respiratory tract infections are the third leading cause of death in the world, according to the World Health Organization (WHO). According to research conducted in 2018 by Riset Kesehatan Masyarakat (*Riskesdas*), pneumonia occurs in Indonesia at a rate of 1.8% and 4.5%, respectively.^{1–4}

The use of herbal ingredients has been widely developed as an additional therapy to help cure various diseases. Since ancient times, garlic has been utilized as a food additive and a traditional remedy throughout the world. Garlic has shown a variety of positive effects, including

immunomodulatory, antibacterial, and anti-inflammatory properties, as stated in studies conducted in vitro in the lab and in vivo on humans and experimental animals by Arreola et al and Bhatwalkar et al. The administration of garlic as an adjunct therapy has the potential to provide better outcomes in patients with pneumonia.^{5–7}

A pleiotropic cytokine called interleukin-6 (IL-6) contributes to infection. Increased IL-6 in the blood indicates the presence of an ongoing inflammatory condition, so IL-6 can be used as an inflammation marker, can predict mortality and morbidity, and is useful in evaluating the success of patient treatment. Neutrophils, which make up between 40% and 60% of the white blood cell population, are the body's primary line of defense against infections like bacteria.^{6–8}

In an infection, neutrophils that are dormant in a healthy person's circulation can become active.

Activated neutrophils will migrate to the site of infection to assist in fighting pathogenic microorganisms. The findings of this investigation should demonstrate the significance of garlic in reducing excessive inflammation in pneumonia by reducing IL-6 levels and neutrophil levels to reduce patient mortality and morbidity and shorten the duration of hospitalization for pneumonia patients.⁶⁻⁸

METHODS

A quasi-experimental research methodology was employed. It was determined how much IL-6 and neutrophils were present using pre- and post-test control group designs. The length of the hospital stay was evaluated using a posttest-only control group approach. The research subjects were pneumonia patients who underwent treatment at Dr. Moewardi General Hospital, Surakarta since August 2022 until the number of samples was fulfilled. The research sample was established through successive sampling. In this investigation, a sample size of 20 samples was employed for both the treatment and control groups.

Pneumonia patients who were hospitalized at Dr. Moewardi General Hospital, Surakarta and met the inclusion and exclusion criteria were given education, asked to sign an informed consent form, recorded identity, smoking history, other illnesses suffered, and other information on the form provided. The subject's initial data were obtained from history-taking, physical examination, blood laboratory, and chest X-ray. In this study, the selected subjects were those with PSI scores ≥ 70 . Subjects were also examined for IL-6 and neutrophil levels from venous blood sampling.

The patients were subsequently randomized into two groups at random; the treatment group received standard treatment based on guidelines for pneumonia by the Indonesian Society of Respiriology (ISR) along with 350 mg of garlic daily for six days, while the control group only received standard treatment. Antibiotics and other supportive therapy were administered to all subjects according to empirical therapy and might be changed to definitive

therapy after adjusting for culture data based on guidelines for pneumonia by ISR.

Patients who experienced garlic side effects that improved with symptomatic therapy would continue to be included in the study, while patients who did not improve with symptomatic therapy would be discontinued from the study and given therapy until the side effects improved. The patient was then followed up until a stable clinical condition was achieved. Patients were taken venous blood samples again for the examination of IL-6 and neutrophils on day 6, at least 6 hours after consuming garlic capsules. The therapeutic response after administration of garlic was measured based on the decrease in IL-6 levels, neutrophil levels, and length of hospitalization.

This research was approved by the ethical committee of Dr. Moewardi General Hospital, Surakarta before the research was conducted. Data analysis was carried out on Windows using SPSS version 21. The existing data was tested using the Shapiro-Wilk normality test, then the research variables were tested using an independent t-test and Mann-Whitney test.

RESULTS

This study was conducted on 40 pneumonia patients treated at Dr. Moewardi General Hospital, Surakarta from August 2022 to October 2022. The subjects in this study were divided into a treatment group and a control group. The treatment group received standard therapy and garlic once daily for six days; the control group only received standard therapy.

While the treatment group received standard therapy based on guidelines along with 350 mg of garlic once daily for six days, the control group only received standard therapy. Variable characteristics of research subjects were measured in each group. The homogeneity assessment of the research variables was carried out as a condition for the feasibility of clinical trial research procedures. The significance limit between the two groups, if the value of $P < 0.05$, then the two groups are said to be

homogeneous. The basic characteristics of the research subjects can be seen in Table 1.

Table 1. Basic Characteristics of Research Subjects

Basic Characteristic	Groups		P
	Treatment	Control	
Sex			
Female	10 (50.0%)	8 (40.0%)	0.525
Male	10 (50.0%)	12 (60.0%)	
Age	55.90±13.92	57.50±16.85	0.378
PSI Score	81.50±19.42	82.70±12.85	0.819
Occupation			
Housewife	6 (30.0%)	8 (40.0%)	0.780
Merchant	3 (15.0%)	3 (15.0%)	
Driver	1 (5.0%)	1 (5.0%)	
College student	1 (5.0%)	1 (5.0%)	
Construction labourer	0 (0.0%)	1 (5.0%)	
Office Employee	0 (0.0%)	1 (5.0%)	
Farmer	2 (10.0%)	2 (10.0%)	
Retired	2 (10.0%)	0 (0.0%)	
Not working	5 (25.0%)	3 (15.0%)	
Smoking history			
Negative	11 (55.0%)	13 (65.0%)	0.519
Positive	9 (45.0%)	7 (35.0%)	
Comorbid			
Ascites	2 (10.0%)	1 (5.0%)	0.387
Cholelithiasis	0 (0.0%)	2 (10.0%)	
Discarded covid-19	2 (10.0%)	4 (20.0%)	
Pleural effusion	3 (15.0%)	2 (10.0%)	
Hemoptysis	0 (0.0%)	2 (10.0%)	
Hypertension	2 (10.0%)	2 (10.0%)	
Melena	1 (5.0%)	1 (5.0%)	
CHD	2 (10.0%)	0 (0.0%)	
COPD	2 (10.0%)	0 (0.0%)	
Peptic Ulcer	1 (5.0%)	1 (5.0%)	
Vertigo	2 (10.0%)	0 (0.0%)	
Others	3 (15.0%)	5 (25.0%)	

The variables assessed in this study were IL-6 levels, neutrophil levels, and length of hospitalization. Samples of venous blood were taken to examine levels of IL-6 and neutrophil, while the length of hospitalization was calculated from the time the patient was admitted until the patient was discharged in days. The characteristics of this research variable can be seen in Table 2.

We observed that the treatment group (-3878.90±3271.79) experienced more neutrophil decline than the control group (-1813.65±4527.84) and the comparison of the differences in neutrophil decline showed a significant difference in statistics; the value of $P=0.025$.

Table 2. Characteristics of Research Variable

Basic Characteristic	Groups		P
	Treatment	Control	
IL-6 level	146.69±151.63	97.05±156.37	0.234
Neutrophil level	13525.90±5210.53	11858.90±7520.05	0.123
Length of stay	7.35±0.99	7.35±1.09	0.876

According to the study's findings, the treatment group (-93.58±128.14) had a higher decrease in IL-6 than the control group (-29.91±173.42), and a statistically significant difference between the two groups was identified, showing a value of $P=0.027$. As a result, adding garlic therapy to pneumonia treatment is successful in lowering IL-6 levels.

Table 3. IL-6 Level Before Treatment, After Treatment, and IL-6 Difference

Groups	IL-6		P	IL-6 difference
	Pretest	Post-test		
Study	146.69±151.63	53.11±58.14	0.003	-93.58±128.64
Control	97.05±156.37	67.14±78.0	0.881	-29.91±173.42
P	0.234	0.665		0.027

The average subject length of stay was 7.35±0.99 days in the treatment group, while the average for subjects in the control group was 7.35±1.09 days. As a result, there was no difference in length of stay between patients in the treatment group and the control group. The statistical test yielded a value of $P=0.876$, indicating no difference between treatment and control groups in terms of the average length of stay for participants.

Table 5. Difference in length of stay in control and study group

Variable	Groups		P
	Study	Control	
Length of stay	7.35±0.99	7.35±1.09	0.876

Table 4. Neutrophil Level Before Treatment, After Treatment, and Neutrophil Difference

Groups	Neutrophil		P	Neutrophil difference
	Pretest	Post-test		
Study	13525.9±5210.53	9647.0±3914.68	<0.001	-3878.9±3271.79
Control	11858.9±7520.05	10045.25±3815.19	0.191	-1813.65±4527.84
P	0.123	0.746		0.025

DISCUSSIONS

The use of biological markers such as IL-6 and neutrophils, as well as the use of a scoring system such as the PSI, can guide the severity assessment of pneumonia and the decision between outpatient or inpatient care. The use of appropriate antibiotics is very important for healing and preventing the worsening of pneumonia patients. Giving additional therapy with anti-inflammatory effects in pneumonia patients, such as garlic, is expected to reduce the inflammation that occurs. IL-6 levels, neutrophil counts, patient length of stay, and comparisons between the treatment group and the control group were used to measure the reduction in inflammation.

A total of 40 subjects participated in this trial; 20 were in the control group and 20 were in the treatment group. There were 22 male and 18 female participants in this study, making up the subjects' gender. In this study, more male than female subjects were acquired; this is comparable to a study by Rahayu on pneumonia patients in 2020, in which 61% of the individuals were male. One of the risk factors for pneumonia is that men are more likely to smoke and be exposed to it at work than women.⁹

The average age of the participants in the treatment group was 55.90 years, whereas it was 57.50 years in the control group. Age-based differences in the characteristics of research participants between the two groups were not significant statistically. This study's findings about subjects' mean age were similar to a study by Ramlie et al in 2022 on pneumonia patients, who discovered that the subjects' age in the study was 57–59 years.¹⁰ Because older individuals' immune systems are weakened and their airways change as they age and develop concomitant conditions, old age may be one of the variables that affect the incidence of pneumonia.^{9,10}

The average PSI score of patients in the treatment group was 81.50 ± 19.42 , and in the control group, the average was 82.70 ± 12.85 . The statistical test result yielded a value of $P=0.819$, indicating no discernible difference between the treatment and control groups in terms of PSI scores. The average

PSI value obtained in this study was similar to the study by Yudhawati and Yuniawati in 2021 which found the average PSI score was 88.58 in pneumonia patients.¹¹ The PSI score can be used to determine the risk, mortality rate, and type of treatment received by the patient.^{11,12}

Subject occupation in this study obtained similar results between the control and treatment groups. Statistical analysis pointed out a value of $P=0.78$, indicating that there was no difference between the two groups in the characteristics of the research subjects based on occupation. Research subjects showed a wide variety of comorbidities. Discarded COVID-19 was the most common comorbid. The statistical test yielded a value of $P=0.387$, indicating that there were no appreciable differences in the comorbidity-based characteristics of the research subjects between the two groups; and this result is similar to a research conducted in 2020 by Rahayu.^{9,13}

Patients in the treatment and control groups were found to have nearly identical smoking histories: nine patients (45.0%) in the treatment group and seven patients (35.0%) in the control group. There were no significant differences in the smoking history-based features of the research subjects between the treatment and control groups ($P=0.519$). A history of cigarette smoke exposure can cause mucociliary damage and inflammation in the respiratory tract which can facilitate the occurrence of pneumonia. This result is identical to the previous study by Rahayu in 2020 where smoking history was not significantly different based on statistics.⁹

On the first day of the investigation, IL-6 levels were assessed before the subject consumed garlic and on the sixth day after the subject consumed garlic for 6 days. The results showed that the treatment group experienced a decrease in IL-6 more than the control group, which had a value of $P=0.027$ which was significant statistically. As a result, adding garlic therapy to pneumonia treatment is effective in reducing IL-6 levels.

Bacterial infection can be caused by both gram-positive and gram-negative bacteria; it is the most prevalent cause of pneumonia which causes

acute inflammation of the lung parenchyma.¹⁵ Infectious microorganisms produce PAMPs such as lipopolysaccharides (LPS), lipoteichoic acid (LTA), and peptidoglycans, as well as DAMPs that can trigger the activation of various pattern recognition receptors (PRR), especially TLR-4 and TLR-2. PRR activation due to PAMP and DAMP then activates lung epithelial cells, alveolar macrophages, and NF- κ B. Proinflammatory cytokines such as IL-4, TNF- α , IL-6, IFN- γ , and chemokines are produced when lung epithelial cells, alveolar macrophages, and NF- κ B are activated.^{14,15}

Immune dysregulation that occurs in pneumonia patients causes an immune response that should be a defense response against pathogenic microorganisms but worsens the existing condition. Excessive and uncontrolled inflammatory reactions and inadequate eradication of pathogenic microorganisms cause pneumonia to develop into more severe cases. High levels of IL-6 in patients may indicate ongoing inflammation and are associated with clinical symptoms and the severity of pneumonia.^{15,16}

Shang et al stated that garlic and its organosulfur content, especially allicin, have anti-inflammatory, immunomodulatory, and antimicrobial activities. Garlic works by reducing NF- κ B activation, thereby reducing IL-6 production and other inflammatory mediators and chemokines.¹⁷ Garlic prevents the production of COX-2 and PGE2 through inactivation of NF- κ B, and garlic also inhibits the migration of neutrophilic granulocytes into the epithelium.^{17,18}

The results of this study are similar to those of Arreola et al, who discovered that the organosulfur content of garlic can provide an immunoregulatory effect and affect immune cells so that it can reduce proinflammatory cytokine levels like IL-6. The results of this study are also identical to those of Shang et al who also observed that garlic could inhibit inflammation, especially by inhibiting the mediators of inflammation such as IL-6, IL-1, and TNF- α , so that it has good potential as a therapy in inflammatory diseases.^{6,17}

Neutrophil levels were measured on the first

day of the study before the subject consumed garlic and on the sixth day after the subject consumed garlic for 6 days. The results showed that the treatment group experienced a decrease in neutrophils more than the control group, and it was statistically significant. Thus, the addition of garlic therapy is effective in reducing neutrophil levels in pneumonia patients.

Giving garlic to pneumonia patients causes proinflammatory cytokines such as IL-6 to decrease so that neutrophil activation will be reduced. Excessive production, activation, and recruitment of neutrophils causes more severe lung tissue damage by ROS, RNS, and proteases produced by neutrophils. Garlic also inhibits the migration of neutrophilic granulocytes into the epithelium, thereby contributing to the reduction of inflammation in lung tissue.^{19,20}

Neutrophils are the body's main defense against bacteria and other pathogens, comprising 40–60% of the total number of white blood cells. In the circulation of a normal person, neutrophils stay in a resting state. Neutrophil toxic substances are not released at rest, so they do not damage tissues. Bacterial byproducts and cytokines or chemokines, such as IL-6, TNF- α , GM-CSF, and IFN- γ , stimulate neutrophils when they are at rest. Then, activated neutrophils are sent to the area of infection or inflammation, where they look for signals that will cause them to start killing germs. Membrane receptors for complement proteins and immunoglobulins near the infection site will identify and attach to opsonized bacteria, causing the creation of pseudopodia, phagocytosis of pathogens, and eradication within intracellular phagosomes. Neutrophils have protease reserves and can create ROS and RNS to quickly phagocytose infections, but if these poisonous chemicals are released in excess by neutrophils, they can potentially harm tissues.^{14,16}

The results of this study are similar to those of Alam et al, who pointed out that administration of the main organosulfur content of garlic significantly reduced neutrophil levels with $P < 0.05$ in the treatment group, and also reduced IL-6 levels. Schepetkin et al investigated the immunomodulatory

activity of neutrophils and observed that the organosulfur content of garlic could suppress the production of ROS by neutrophils. Garlic's organosulfur content may be an effective therapeutic modulator of the innate immune response.^{21,22}

The average treatment group length of stay was 7.35 ± 0.99 days, whereas it was 7.35 ± 1.09 days in the control group. As a result, there was no length of stay difference between the two groups. The statistical test shows a value of $P=0.876$, indicating no significant difference between the treatment and control groups in terms of the average duration of stay for patients. The patient's length of stay was unaffected by the inclusion of garlic therapy.

In this study, a stay lasted an average of 7.35 days. This outcome is comparable to a study in 2020 by Ramlie et al, who discovered that pneumonia patients spent an average of 7.15 days in the hospital. However, the two studies were not identical. The treatment and control groups in this trial did not differ in a way that was statistically significant on the length of stay following ISR's recommendations for pneumonia diagnosis and treatment. Treatment duration is generally 7-10 days in patients who show improvement in the first 72 hours. Administration of antibiotics in pneumonia for at least 5 days. The length of hospitalization should be shortened by changing the injection to oral, followed by outpatient treatment; this is to reduce treatment costs and prevent nosocomial infections.^{1,2,10}

The findings of this study are comparable to those of studies by Dwikuntari on 30 pneumonia patients who were treated at Dr. Moewardi General Hospital. Dwikuntari investigated the vitamin C effect on procalcitonin and length of hospital stay, which found no significant length of stay difference between the two groups. The results showed no difference in length of hospital stay; this could be due to other comorbidities or diseases that might prolong their length of stay. Abnormalities in the heart, kidneys, brain, and other organs were found in both study groups. Clinical improvement in pneumonia may not be in line with improvement in other comorbidities or comorbidities, thus affecting patient length of stay. Menendez et al found that the length of stay for

pneumonia patients was influenced by multiple factors, especially the severity of pneumonia and the presence of comorbid conditions, as well as non-clinical factors such as waiting time for investigations and the "weekend effect".^{1,23,24}

LIMITATIONS

Some research subjects were hospitalized not only because of pneumonia but also due to other indications such as abnormality of the heart, kidney, neurology, and other diseases, so the subjects' length of stay does not always reflect the time of pneumonia improvement.

CONCLUSIONS

There were significant differences in IL-6 and neutrophil levels in pneumonia patients; subjects who received garlic had a significant decrease in IL-6 and neutrophil levels. It showed the effectiveness of garlic in reducing inflammation in pneumonia patients. There was no difference in the length of hospitalization for both subject groups; this might occur due to the fact that not all subjects were only hospitalized with a diagnosis of pneumonia but also with other diseases and comorbidities that could cause lengthening of hospitalization.

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