# **Correlation between NLR and Ferritin in COVID-19 Patients in ICU Dr.** Kariadi Hospital

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## ABSTRACT

COVID-19 infection is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Diabetes mellitus and heart disease comorbid have high morbidity and mortality. Increased Neutrophils to Lymphocyte Ratio (NLR) and ferritin assist in early screening of disease severity, especially in the Intensive Care Unit (ICU). This study aimed to determine the relationship between NLR and ferritin in COVID-19 patients in the ICU. The study was an analytical observational with a cross-sectional approach from July to October 2020 at the Laboratory of Clinical Pathology and Medical Records at Dr. Kariadi Hospital, Semarang. Pearson correlation test was used and significance p<0.05, r 0.3<r<0.5 were obtained. Neutrophils-lymphocyte ratio and ferritin mean value of NLR and ferritin were 13.91 and 1675, respectively. There was a correlation between NLR and ferritin in COVID-19 patients in the ICU with p=0.012 and r=0.437. Increased NLR of COVID-19 patients occurs due to infiltration of the innate and adaptive immune system in infected tissue, resulting in decreased circulating lymphocytes and disturbed proliferation due to increased ferritin as an acute phase reactant protein. This subsequently increases NLR and ferritin in COVID-19 in the ICU. This study found a moderate positive correlation between NLR and ferritin in COVID-19 in the ICU.

Keywords: Neutrophils lymphocyte ratio, ferritin, COVID-19

# INTRODUCTION

Coronavirus Disease or COVID-19 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This pneumonia was declared a pandemic by WHO on March 11, 2020. As of July 9, 2020, WHO reported 11,84,226 confirmed cases with 545,481 deaths worldwide (Case Fatality Rate/CFR was 4.6%). Indonesia reported its first case on March 2, 2020. As of July 9, 2020, the Ministry of Health reported 70,736 confirmed cases of COVID-19 with 3,417 deaths (CFR 4.8%).<sup>12</sup>

This disease causes various clinical manifestations in infected patients, from mild disease without specific symptoms to severe pneumonia with impaired organ function. The severity resulting from this viral infection becomes a very valuable reason to early determine the risk factors for death of patients with severe SARS-CoV-2 infection as decision-making interventions to increase cure rates and better quality of prognosis.<sup>34</sup>

The physiological immune response of circulating leukocytes to various stressful events is characterized by an increased number of neutrophils and decreased number of lymphocytes. Neutrophils to Lymphocyte Ratio (NLR) has a strong determinant value in predicting bacteremia. The use of NLR also varies, it is used as a diagnostic tool for appendicitis, additional predictive markers of severe sepsis and septic shock in the oncology ICU, as well as cardiovascular disease. In addition, NLR determinations are easy to determine and widely available at most laboratories.<sup>4</sup>

The majority of COVID-19 patients showed laboratory results for lymphopenia and increased levels of infection-related biomarkers, such as higher neutrophil count.<sup>5</sup> A study by Liu showed that increased NLR was the sole risk factor for mortality and could help identify high risk in patients with COVID-19.<sup>6</sup> In addition, it was also found that several risk factors such as hypertension, diabetes, Congestive Heart Disease (CHD) were associated with mortality and were positively correlated with the risk of death in the hospital.

A severe manifestation of COVID-19 infection is Acute Respiratory Distress Syndrome (ARDS), which is triggered by Cytokine Release Syndrome (CRS). Cytokine release syndrome also triggers secondary hemophagocytic lymphohistiocytosis (sHLH). Associated with elevated serum cytokines, high ferritin concentration is one of the characteristics of sHLH. sHLH is known as macrophage activation syndrome. A retrospective study of COVID-19 patients found that elevated ferritin and IL-6 were associated with patient mortality.<sup>7,8</sup>

This study aimed to determine the relationship between the ratio of neutrophils to lymphocytes ratio and ferritin in COVID-19 patients in the ICU.

#### **METHODS**

The study was conducted retrospectively with an observational approach (cross-sectional) from July to October 2020 at the ICU Dr. Kariadi Hospital, Semarang. The research data were taken from the medical records of patients who were confirmed positive for COVID-19 by consecutive sampling. The NLR value was obtained from the calculation of the number of neutrophils divided by absolute lymphocytes. Inclusion criteria were male and female patients with ages ranging from 30 to 75 years with

Table 1. Characteristics of research subjects

positive swab/PCR test results. Exclusion criteria were pregnant women, liver disease, history of malignancy, radiation therapy/chemotherapy, autoimmune, and HIV.

The sample size in this study was 32 people. Research permission was obtained from the Medical And Health Research Ethics Committee of Dr. Kariadi Hospital, Semarang with number 643/EC/ KEPK-RSDK/2020.

#### **RESULTS AND DISCUSSIONS**

A total of 32 COVID-19 patients in the ICU of Dr. Kariadi Hospital were selected according to the inclusion and exclusion criteria of the study. The characteristics of the research subjects are presented in Table 1. The subjects in this study consisted of a higher number of males (56.3%) than females (43.8%) and the mean age was 55 years. Comorbidity in the study sample was hypertension (71.9%) followed by diabetes mellitus (68.8%). The mean NLR was 13.91 and the mean ferritin was 1674.

Variable (n=32)	Mean±SD	Median (min-max)	
Gender	Male 18 (56.3%)		
	Fem	ale 14 (43.8%)	
Diabetes mellitus	Yes 22 (68.8%)		
	No	10 (31.3%)	
Hypertension	Yes 23 (71.9%) No 9 (28.1%)		
Age (years)	56.31±9.946	55 (32-75)	
Neutrophils (%)	86.22±5.945	87 (66-96)	
Lymphocytes (%)	8.50±4,732	7.5 (2-26)	
NLR	13,9116±9,38188	11,335 (2.54-48)	
Ferritin (ug/dL)	1674,9538±1093,55878	1489,215 (314,11-4653,23)	
SGOT (U/L)	55.19±29,050	47.5 (19-131)	
SGPT (U/L)	45.97±23,352	41.5 (10-95)	
Hemoglobin (g/dL)	12,031±2,0292	11.45 (7.8-17.4)	
Mean corpuscular volume (fL)	29,222±1,7832	29.5 (25.2-32.0)	
Mean corpuscular Hemoglobin(pg)	86,594±5,2378	87.25 (76.6-94.8)	

Abbreviations: SD (Standard Deviation); min (minimum); max (maximum), SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvate Transaminase

Table 2.	Correlation	between	NLR	and	ferritin
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Variable	Fer	ritin (µg/dL)	Interpretation
variable	р	r	
NLR			P<0.05 was significant,
	0.012*	0.437	r=0.437 was moderately positive

Pearson test, \*p< 0.05; r, correlation coefficient; NLR, Neutrophils Lymphocytes Ratio



Figure 1. Scatter plot of correlation between NLR and ferritin in COVID-19 patients

Based on the results of Pearson's analysis, a moderate positive relationship was found between NLR levels and ferritin (p=0.012; and r=0.437) (Table 2), and the correlation between NLR and ferritin is presented in Figure 1.

Coronavirus binds to host cell receptors via spike proteins and the host receptor Angiotensin-Converting Enzyme 2 (ACE2), which is expressed in large amounts in the lung, heart, ileum, kidney, and bladder tissue.<sup>9</sup>

Research subjects in this study consisted of a higher number of males (56.3%) than females (43.8%) and the mean age was 55 years. The mean of NLR and ferritin was 13.91 and 1674, respectively. The most comorbid disease found in this study was hypertension (71.9%), followed by diabetes mellitus (68.8%). In addition, the mean value of the enzyme SGOT and SGPT was 55.19 and 45.97, respectively.

Increased NLR was significantly correlated with an increased risk of death during hospitalization. A study by Liu found that increased NLR was the sole risk factor for mortality and can help identify high risk in COVID-19 patients with several risk factors associated with mortality such as hypertension (OR=3.94, p=0.03) and diabetes (OR=3.30, p=0.0168), which were positively correlated with the risk of death in the hospital. A cohort study by Qin et al. found that 44% of patients infected with COVID-19 had at least one comorbid disease. The decreased lymphocytes count in COVID-19 infection is associated with dysregulation of the immune system due to both risk factors and the pathogenesis of COVID-19 and infiltration of adaptive cytotoxic CD8+ cells due to chemoattractant neutrophils and lymphocytes IL-8, which are produced by infected epithelium.5,6

Ferritin is a nonspecific inflammatory marker as an acute phase response consisting of H subunits and L subunits called FTH (ferritin heavy chain) and FTL (ferritin light chain). The increase of serum ferritin during inflammation can be caused by macrophages, especially FTH, which has immunomodulatory effects, including suppression of delayed-type hypersensitivity to trigger energy, suppression of antibody production, decreased phagocytosis by granulocytes, and regulation of granulomonocytopoiesis.<sup>10</sup>

A study by Pastora reported that ferritin levels in seriously ill COVID-19 patients were 3-4 times higher compared to those in survivors.<sup>8</sup> In addition, Liu *et al.* reported a decrease in IL-6 and ferritin in patients during recovery.<sup>6</sup>

Human T and B lymphocytes bind FTH directly, although the exact receptor is unknown. This binding has an immunosuppressive effect in-vitro by interfering with T cell proliferation and B cell maturation and immunoglobulin production. The inhibitory function of FTH is largely mediated by IL-10. In the presence of CXCL12, ferritin binds to CXCR4 directly and induces IL-10 synthesis. According to this study, an increase in NLR and serum ferritin was found in COVID-19 patients in the ICU.<sup>10</sup>

The mean value of Hb, MCV, and MHC in this study was 12.03, 29.2, and 86.5; respectively. Hb <10 g/dL was found in 4 patients in this study who suffered from complications of upper gastrointestinal bleeding and a diagnosis of COVID-19 coagulopathy. However, there were no hematological and ferritin data for these patients before COVID-19 infection, making a comparison impossible in this study.

No comparative data on serum ferritin of patients before COVID-19 infection and determination of exclusion and inclusion factors based on medical records remained the limitations in this study, leading to a possibility that patients with iron storage disorders might affect serum ferritin levels.

## **CONCLUSIONS AND SUGGESTIONS**

The results of this study found a moderate positive relationship between NLR and ferritin in COVID-19 patients in the ICU.

It was necessary to perform further research involving a larger number of samples and sample selection by considering the variable of iron deficiency anemia.

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