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RESEARCH **Open Access**

Comorbid Description and Neutrophil Lymphocyte Ratio in COVID-19 Patients (Suspect and Confirmed Patients)

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Abstract

Neutrophil Lymphocyte Ratio (NLR) is a laboratory available as a marker used for the evaluation of systemic inflammation, NLR is a significant predictor and is a critical prognosis for COVID-19 infection and can serve as a useful factor to reflect the intensity of the imbalance of inflammation and immune response in COVID-19 patients. This study aims to determine the difference in NLR values in negative and confirmed COVID-19 patients and description for comorbid for both. This study is an analytic observational study with a cross-sectional design. The study sample was 423 suspected COVID-19 patients at hospitals in Cilacap district for the period in March – October 2020. The data obtained were analyzed descriptively and using the fisher-exact test. In these results from suspected patients with negative COVID-19, lung illness were present 31.8%, viral infections 22.9%, other respiratory disorders 6.1%, diabetes mellitus 4.7%, and anemia 4.7%. Whereas suspected patients with confirmed COVID-19 were, without comorbid diseases (40.2%), lung disease (12.4%), diabetes mellitus (7.7%), hypertension (6.2%), and other respiratory illnesses (5.2%). The mean of NLR in confirmed patients is 3.57 but not any difference between negative and confirmed patients COVID-19, but there's any a relationship between NLR and ARDS conditions.

Keywords: NLR, RT-PCR, COVID-19.

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1. INTRODUCTION

In December 2019, a case of pneumonia with an unknown cause emerged in Wuhan, Hubei Province, China. The first case was linked to a fish market in Wuhan (Rothan & Byrareddy, 2020), (Guo et al., 2020). Five patients were hospitalized from 18 December to 29 December 2019 with symptoms of fever, cough, and dyspnea accompanied by complications of Acute Respiratory Distress Syndrome (ARDS) (Ren et al., 2020).

Historically, the majority of investigations on circulating immune cells in disease have centered on the examination of peripheral blood mononuclear cells, ignoring neutrophils and other granulocytes. Consequently, our understanding of the most numerous and technically challenging subpopulation of immune cells in the blood is lagging. Recent breakthroughs in single-cell omics technology have facilitated the study of this cell population in humans, particularly in diseased circumstances, challenging the notion that neutrophils are a homogeneous population of short-lived cells. Granulocytes, which are part of the innate immune system, are among the first cells recruited to a site of infection. They play a crucial role in determining the first response to an insult and in mediating between the innate and adaptive arms of the immune system. However, if not adequately controlled, the potent effector actions of these cells can cause tissue harm (Jaillon et al., 2020), (Xie et al., 2020), (Ballesteros et al., 2020), (Liew & Kubes, 2019).

Neutrophilia is an expression of a cytokine storm and hyperinflammatory state that has an important pathogenetic role in COVID-19 and related infections such as SARS. Lymphopenia commonly found in patients with COVID-19 represents a compromised immune system against the virus (Frater et al., 2020), (Henry et al., 2020). Neutrophil Lymphocyte Ratio (NLR) is one of the necessary parameters for the prognosis of infection, inflammation, and some types of cancer (Retnoningrum et al., 2018), (Wibisana et al., 2019). NLR is a significant predictor of and a critical prognosis for COVID-19 (Liu et al., 2020), infection and may serve as a useful factor to reflect the intensity of the imbalance of inflammation and immune response in COVID-19 patients (Liu et al, 2020).

Since the onset of the COVID-19 pandemic, substantial data has emerged indicating that neutrophils play a key role in the pathogenesis, particularly in individuals with severe illness histories. Neutrophils were once thought to be a very uniform cell type, but recent research has shown their remarkable transcriptional and functional variety as well as their developmental pathways (Reusch et al., 2021). This research is essential for a better understanding of the different elements of neutrophil participation not just in confirmed COVID-19 patient but in negative cases too. This study aims to determine the difference in NLR values in negative and confirmed COVID-19 patients.

2. RESEARCH METHOD

This study is an analytic observational study, with a cross-sectional design. The research sample was 423 suspected COVID-19 patients who were examined for complete blood using the Hematology Analyzer, then examined by RT-PCR using samples taken from nasopharyngeal and oropharyngeal swabs at hospitals in Cilacap Regency in March - October 2020, this research was have ethical clearance statement from Commission Ethic for Health research of Health Polytechnic of Yogyakarta (e-KEPK/POLKESYO/0571/IX/2020). The data used are secondary data obtained from suspected COVID-19 patients with 214 negative patients and 209 confirmed patients. The secondary data obtained were analyzed descriptively and tested with fisher-exact.

3. RESULTS AND DISCUSSION

Table 1 describe that more man patients are infected with COVID-19 compared to women, namely 105 (50.2%) man while 104 (49.8%) women. This result is in line with Hidayati's research (2020) where man dominate the population with confirmed COVID-19, which accounts for more than half of the total number of those who have been confirmed (Susilo et al., 2020), during this pandemic period, women are more disciplined in undergoing health protocols such as implementing physical distancing, diligently washing hands, and using masks compared to with men (Hidayati, 2020). Male was the strongest predictor of increased plasma ACE-2 concentrations. This suggests that man have higher ACE-2 levels, and is consistent with a poorer prognosis in man with heart failure (Chairani, 2020). Meanwhile, from the distribution of the age group of COVID-19 patients, the highest age range was 46-59 years with 69 patients (33%) and the lowest was 0-5 years with 2 patients (1%). In elderly, the risk of various disorders involving the immune system will increase, for example the risk of suffering from autoimmune diseases, malignancies, so that it will be easier to be infected by this disease (Oudit & Pfeffer, 2020). Another research, show that the most severe COVID-19 effects are observed in older adults with various co-morbidities and individuals with complex underlying health issues (McMichael et al., 2020).

Table 1. Distribution of confirmed COVID-19 patients by age group and sex.

Age Group (Years)	**Frequency (%)**		**Total**
	Man	Women	
0-5	2 (1 %)	0 (0%)	2 (1%)
6-18	13 (6.2%)	12 (5.8%)	25 (12%)
19-30	13 (6.2%)	12 (5.8 %)	25 (12%)
31-45	26 (12.4%)	25 (12 %)	51 (24,4%)
46-59	29 (13.9%)	40 (19.1%)	69 (33%)
≥ 60	22 (10.5%)	15 (7.2%)	37 (17.7%)
Total	**105 (50.2%)**	**104 (49.8%)**	**209 (100%)**

Table 2. Overview of NLR in negative and confirmed COVID-19 patients.

	Mean	**Median**	**Min**	**Max**	**SD**	**p-value**
Negative	4.85	2.86	0.09	31.0	5.55	0.219
Confirmed COVID-19	3.57	2.41	0.21	30.3	3.53	

The average NLR in COVID-19 confirmed patients is 3.57 with a significance value of 0.219, which means there is no difference between the NLR value in COVID-19 negative and positive patients. According to (Liu et al., 2020) the limit of normal value or cut off for NLR in COVID-19 patients is 3.13 (Liu et al., 2020). In this research range of NLR values is very wide because this study uses all samples that meet the inclusion and exclusion criteria without eliminating factors that can affect immune mechanisms such as age (Oudit & Pfeffer, 2020). While in this study using patient data from 0 years of age to 60 years and in the study Yang et al., (2020) stated that NLR increased proportionally with increasing age (Yang et al., 2020).

Table 3. NLR of confirmed COVID-19 patients with non-ARDS and ARDS conditions

		Non ARDS		**ARDS**		**Total**		**p-value**
		Freq	**Percentage %**	**Freq**	**Percentage %**	**Freq**	**Percentage %**	
NLR Value	Normal	131	98.5	2	1,5	133	63,6	0.001
	Non-normal	66	86.8	10	13.2	76	36.1	
	Total	197	94.3	12	5.7	209	100	

In table 3, the results of the Fisher-exact test for analysis the NLR values of confirmed patients with non-ARDS comorbid conditions compared to ARDS obtained a significance value of 0.001 (<0.05), which means that there is a relationship between NLR values and ARDS conditions. The results of this study are the same with Liu et al., (2020) stating that NLR is a predictive factor for predicting the early stage of COVID-19-infected patients who are likely to develop critical illness. NLR may be a reliable marker for evaluating the severity of COVID-19 disease (Liu et al., 2020). Lymphocyte count may be useful for establishing the early diagnosis of ARDS in COVID-19 patients (Peng et al., 2020).

In severe COVID-19 patients are able to produce very high amounts of other proinflammatory cytokines in the peripheral blood, namely GM-CSF, IL-1ß, IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1 and IL-4, which have the potential to cause a cytokine storm. The researchers found that in the lungs of COVID-19 patients with severe severity developed a cytokine storm that made the patient's condition very weak, severe and even death (Tarigan & Arum, 2020).

Table 4. Overview of comorbid disease in suspected COVID-19 patients who are negative, confirmed and died.

Diseases	**Frequency (%)**		
	Negative	**Confirmed**	**Died**
Diabetes Melitus	10 (4.7%)	16 (7.7%)	4 (40%)
Hypertension	5 (2.3%)	13 (6.2%)	0 (0%)
Lung Disease	68(31.8%)	26 (12.4%)	3 (30%)
Hearth Diseases	2 (0.9%)	2 (1%)	0 (0%)
Kidney Diseases	3 (1.4%)	0 (0%)	0 (0%)
Other breathing problems	13 (6.1%)	12 (5.7%)	1 (10%)
HIV & TB	2 (0.9%)	0 (0%)	0 (0%)
Dispepsia	3 (1.4%)	3 (1.4%)	0 (0%)
Myalgia	1 (0.5%)	2 (1%)	0 (0%)
Dermatitis	0 (0%)	1 (0.5%)	0 (0%)
Virus Infection	49 (22.9%)	1 (0.5%)	0 (0%)
Septic Shock	1 (0.5%)	0 (0%)	0 (0%)
Pregnancy	6 (2.8%)	0 (0%)	0 (0%)
Anemia	10 (4.7%)	1 (0.5%)	1 (10%)
Hipoksia	1 (0.5%)	0 (0%)	0 (0%)
Myelitis	1 (0.5%)	0 (0%)	0 (0%)
Ischemia	1 (0.5%)	0 (0%)	0 (0%)
Gastroenteritis	1 (0.5%)	0 (0%)	0 (%)
Headec	1 (0.5%)	0 (0%)	0 (0%)
Depression	0 (0%)	1 (0.5%)	0 (0%)
Diabetes Melitus & CHF	0 (0%)	1 (0.5%)	0 (0%)
Diabetes Melitus & HT	0 (0%)	6 (2.9%)	0 (0%)
No commorbid	16 (7.5%)	84 (40.2%)	0(0%)
Not Any Data	20 (9.3%)	40 (19.1%)	1 (10%)
Total	214 (100%)	209 (100%)	10 (100%)

In table 4, it can be seen that the comorbid conditions of suspected patients who were negative for COVID-19 were lung disease by 31.8%, viral infections 22.9%, other respiratory disorders 6.1%, diabetes mellitus 4.7% and anemia 4. 7%. Meanwhile, the comorbid conditions

of suspected patients with confirmed COVID-19 were in the highest order without co-morbidities (40.2%), lung disease (12.4%), diabetes mellitus (7.7%), hypertension (6.2%) and other respiratory disorders (5.7%). This lung disease consists of pneumonia, tuberculosis, bronchitis, Chronic Obstructive Pulmonary Disease (COPD), asthma and Community-acquired Pneumonia (CAP). Infectious diseases consist of Dengue Hemorrhagic Fever (DHF), HIV, other viruses, dengue fever, herpes, urinary tract infection, cellulitis, diapers and coushing diseases. As for other respiratory disorders consist of flu, pharyngitis, ARDS, acute upper respiratory failure, ARI, common cold, cough and shortness of breath. Based on Yang et al., (2020), Fever occurred in only 43.8% of patients on initial presentation and developed in 83.4% after hospitalization (Yang et al., 2020). Based on research by Sun (2022), the most commonly characteristics of COVID-19 are fever, cough and abnormal chest computed tomography (CT) (Sun et al., 2020). This highly transmittable disease causes pneumonia and other severe respiratory illnesses similar to SARS and MERS (Louis-Jean & Aime, 2020). Such patients may be missed if the surveillance case definition focused heavily on fever detection. Significantly high frequencies of severe cases were observed in patients with diabetes or hypertension. According Peng et al., (2020) stated that NLR has been proven as a marker of diagnostic information and disease severity in pneumonia and bacteremia (Peng et al., 2020).

An increase in NLR indicates an increase in pro-inflammatory cytokines. NLR values can increase in cardiovascular disease, malignancy, diabetes mellitus, and chronic kidney failure. The NLR value of TB patients is higher than normal people. When compared with patients with sarcoidosis, the NLR value of TB patients was higher, but still lower than that of patients with bacterial pneumonia (Peng et al., 2020). Various diseases that cause other chronic inflammation such as diabetes mellitus, cancer, hypertension, and smoking can cause an increase in NLR which is thought to be a cellular response due to endothelial dysfunction (Yang et al., 2020). Low levels of albumin (75.8%, 95% CI 30.5–100.0), high C-reactive protein (58.3%) and high lactate dehydrogenase (LDH) (57.0%) were the most prevalent laboratory results in patients with lymphopenia during the clinical trial. High-Erythrocyte Sedimentation rate (ESR) (41.8%) and low lymphocyte count (43.1%) were also found to be concerning (Guan et al., 2020), (Biscayart et al., 2020), (Huang et al., 2020).

In Indonesia, the majority of patients were male, 30-49 years old, and accompanied by hypertension, diabetes, and heart disease (Sutaryono et al., 2020). Patients who died in this study had a history of diabetes mellitus as much as 40% as shown in table 4. COVID-19 patients with diabetes mellitus had a very severe inflammatory response. This is because COVID-19 causes severe lung dysfunction and inflammation. The entry port of this virus is a special surface glycoprotein on ACE2, the spike. ACE2 is abundant in type II alveolar cells of the lungs. If the amount of ACE2 in COVID-19 patients is excessive, the severity of the disease suffered by the patient also increases, such as can cause ARDS, damage to the liver, heart, kidneys, and even cause death (Cahyadi & Steffanus, 2018). COVID-19 is more severe in chronic patients such as old age, cardiovascular disease, diabetes mellitus, chronic respiratory diseases, hypertension, and cancer (Wu et al., 2020). However, in this study is that there is no patient symptom data that can describe the immune response and has not correlated the results of NLR with the results of examination of other inflammatory marker parameters such as hs-CRP. Is more accurate to evaluate the patient's history, chronic diseases, age, symptoms, CT images, laboratory and RT-PCR test results as a whole (Osman et al., 2020).

4. CONCLUSION

In this study, there was no difference in the results of the Neutrophil Lymphocyte Ratio (NLR) in negative and confirmed COVID-19 patients but there is any relationship between

NLR and ARDS conditions. The mean score of patients with suspected negative COVID-19 is 4.85 and patients with suspected confirmed COVID-19 are 3.57. The NLR can be used as a predictive factor for patients infected with COVID-19 who are likely to develop critical illness. Lung illness was present in 31.8% of putative COVID-19-negative patients, with viral infections in 22.9%, and other respiratory disorders in 6.1%. Patients conditions included non-comorbid diseases (40.2%), lung disease (12.4%), diabetes Mellitus (7.7%) and hypertension (6.2%).

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