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Research

Neutrophil-Lymphocyte Ratio as a Diagnosis Predictor in Pediatric COVID-19 Patients at Dr. OEN Kandang Sapi Hospital, Surakarta, Central Java, Indonesia

Dyah Wulaningsih Retno Edi[1)], Irfan Dzakir Nugroho[2,3)]

[1)]General Practitioner, Dr. Oen Kandang Sapi Hospital, Surakarta
[2)]Department of Pediatrics, Dr. Oen Kandang Sapi Hospital, Surakarta
[3)]Department of Pediatrics, Dr. Moewardi Hospital, Surakarta

ABSTRACT

Background: COVID-19 is a global pandemic and affects all ages, even newborns. Until March 2021, there were 127 million cases of COVID-19 worldwide. In Indonesia, there were almost 1.5 million cases. The main symptoms of COVID-19 are fever and cough, simple laboratory tests such as measuring the neutrophil-lymphocyte ratio (NLR) are also included in the EWS (early warning score) so that they can be used to diagnose COVID-19 with a cut-off limit value of 3.13. The purpose of this study was to determine the value of NLR as a predictor of diagnosis in pediatric patients confirmed by RT-PCR Swab examination at Dr. Oen Kandang Sapi Hospital, Solo, Surakarta.
Subjects and Method: A diagnostic test study that assessed the sensitivity, specificity, negative predictive value and positive predictive value of the NLR value as a predictor of COVID-19 diagnosis in pediatric patients confirmed by RT-PCR Swab examination at the time level of March 2020 - March 2021. Data were taken from electronic medical records of inpatients and sampling was done by consecutive admission sampling.
Results: A total of 153 study subjects with 34 PCR (+) patients and 119 PCR (-) patients. The characteristics of the study sample were seen from gender, age, symptoms, chest x-ray and patient outcomes. The NLR cutoff limit value for pediatric COVID-19 patients is 1,625 with an AUC (area under curve) of 0.504. The NLR value of 1.625 has a sensitivity of 0.588 (58.8%) and a specificity of 0.513 (51.3%). The PPV (positive predictive value) was 0.256 (25.6%), the NPV (negative predictive value) was 0.813 (81.3%), the PPR (positive predictive ratio) was 1.207 and the NPR (negative predictive ratio) result was 0.803.
Conclusion: The NLR cutoff value of 1,625 with a sensitivity of 58.8% cannot be used as a predictor of COVID-19 diagnosis in pediatric patients at Dr. Oen Kandang Sapi Hospital, Solo, Surakarta.

Keywords: COVID-19, children, pediatrics, diagnostic lab, NLR, neutrophil to lymphocyte ratio

Correspondence:
Dyah Wulaningsih Retno Edi. General Practitioner, RS Dr. Oen Kandang Sapi Solo, Surakarta. Email: wulandkd@gmail.com.

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BACKGROUND

On December 31, 2019, China reported a mysterious case of pneumonia with an unknown cause. With cases that continue to increase from 44 patients to millions of cases. After being investigated, the sample results showed a new type of coronavirus infection, therefore, it is called SARS-CoV-2 or better known as COVID-19 (Coronavirus Disease 2019) (Makmun & Ramadhani,

2020). COVID-19 is a disease that causes a global pandemic and attacks all ages, even newborns. Until March 2021, there were 127 million cases of COVID-19 worldwide and Indonesia reached 1.5 million cases (COVID-19 TASK FORCE, 2021).

COVID-19 can also attack anyone, elderly individuals with many comorbidities who experienced moderate to severe symptoms and can infect/have vertical transmission. In the case of children/pediatrics, almost 90% experienced mild to moderate symptoms compared to adult patients. Fever and cough are the main symptoms of COVID-19. In patients with moderate to severe symptoms, it can progress rapidly to worsening conditions such as acute respiratory distress, metabolic acidosis, coagulopathy and septic shock. Even patients with symptoms other than respiratory or no symptoms at all can contract COVID-19 disease (PDPI et al., 2020).

Early identification is needed to predict the condition of patients who are at risk for worsening symptoms to become more severe. Investigations can start from laboratory tests such as measurement of the neutrophil-lymphocyte ratio (NLR) which can be used to determine the prognosis of patients in various clinical situations. An increase in the neutrophil-lymphocyte ratio is associated with the severity of the disease and can be considered as an independent biomarker to indicate a poor outcome. The calculation of the NLR value is also included in the COVID-19 Early Warning Score (EWS) so that it can be used in diagnosing COVID-19 patients with a cutoff limit value of 3.13 (Amanda, 2020; Anggraini, 2020; Aryati, 2020).

COVID-19 itself can attack any age even newborns, and a simple lab test such as NLR can help to diagnose COVID-19. This study aims to determine the NLR value as a predictor of COVID-19 diagnosis in pediatric patients confirmed by a reference standard examination, namely Swab RT-PCR at Dr. Oen Kandang Sapi Hospital, Solo, Surakarta.

SUBJECTS AND METHOD

1. Study Design

This is an observational analytic study using a diagnostic test approach to the NLR value in diagnosing COVID-19 confirmed by RT-PCR Swab examination conducted at Dr. Oen Kandang Sapi Hospital, Solo, Surakarta. The sample was taken using the consecutive admission sampling method which was taken based on pediatric patients who were hospitalized from March 2020 to March 2021.

2. Population and Sample

The inclusion criteria in this study were all pediatric patients (aged 0-18 years old) admitted to the inpatient unit who performed RT-PCR Swab at least 2 times to diagnose COVID-19. These patients performed laboratory analysis to see the value of NLR during/before admission to the isolation ward. Meanwhile, the exclusion criteria were pediatric patients who did not undergo simultaneous RT-PCR Swab 2x and incomplete laboratory data.

3. Study Variable

The independent variable was NLR. The dependent variabe was COVID-19 status.

4. Operational Definition of Variable

NLR is a neutrophil-lymphocyte ratio that functions as a biomarker of systemic inflammatory status. Laboratory tests were obtained from the number of neutrophils divided by the number of lymphocytes. In this study, the cut-off used to help diagnose COVID-19 was >3.13.

PCR, also known as Swab RT-PCR (Reverse Transcription - Polymerase Chain Reaction) is a laboratory examination that aims to confirm the diagnosis of COVID-19 by taking mucus samples taken through the nose (nasopharynx) and or mouth (oropharynx).

Pediatrics or commonly called children are someone who has not reached the age of 18 (eighteen) years old.

5. Data Analysis

The variables were measured at the same time with a cross-sectional approach. Data analysis using SPSS 17.0 program, all variables were divided into PCR (+) and PCR (-) groups and then statistically analyzed with $p<0.05$ considered significant. An analysis with the ROC curve was carried out to determine the cutoff value of the NLR then it was tabulated and analyzed again in the 2x2 table to determine the sensitivity, specificity, positive predictive value, negative predictive value, positive predictive ratio and negative predictive ratio.

6. Research Ethics

Data were taken from the patient's electronic medical record, from identity, age, gender, symptoms at admission, chest X-ray/chest plain photo, laboratory results (NLR values) and RT-PCR swab results. This study has been approved by the ethics committee of Dr. Oen Kandang Sapi Hospital, Solo, Surakarta.

RESULTS

The results of the study in a total of 153 study samples were divided into 2 groups, specifically 34 patients with PCR (+) or confirmed COVID-19 and 119 patients with PCR (-). With 94 male patients (61.4%) and 59 female patients (38.6%). The age range in this study was divided into two, with the highest frequency in the age range of 0-5 years by 118 patients (77.1%). Of the 153 samples, 67 patients (43.8%) had respiratory symptoms (fever, runny nose, sore throat, shortness of breath, etc.) and 86 patients (56.2%) had no respiratory symptoms (convulsions, nausea and vomiting, diarrhea, abdominal pain, etc.). All patients also underwent chest X-ray/chest plain X-ray, and most of the results showed the infection of bronchopneumonia in 107 patients (69.9%) which can be seen in Table 1.

Patient outcomes during hospitallization were discarded (went home in good condition and negative evaluation PCR results) by 108 patients (70.6%), self-isolation was 16 patients (10.5%) and there were 26 patients (17%) of PICU transfer and 3 patients (2%) were referred.

From the results of the analysis, there are three variables, namely symptoms, x-rays and outcomes that have a significant relationship with PCR, because they have a $p<0.05$. Based on the ROC curve and Table 2, the results of the AUC (area under curve) of the NLR examination were 0.504 and the cutoff value of the NLR in this study was 1.625 with a p analysis of 0.939 ($p<0.05$). These results indicate that NLR is less accurate as a predictor of COVID-19 diagnosis in pediatric patients. Meanwhile, the NLR ratio in subjects who were positive for COVID-19 ranged from 0.04 to 6.8 with a mean value of 2.23 and a median of 1.98.

Based on Table 4, it can be seen that the NLR examination with a cutoff of 1.625 has a sensitivity of 0.588 (58.8%) and a specificity of 0.513 (51.3%). The PPV (positive predictive value) was 0.256 (25.6%), the NPV (negative predictive value) was 0.813 (81.3%), the PPR (positive predictive ratio) was 1.207 and the NPR (negative predictive ratio) result was 0.803. Diagnostic test results were also carried out with the cutoff commonly used, which was 3.13. The results obtained were 26.5% sensitivity, 71.4% specificity, 0.209 PPV, 0.773 NPV, 0.926 PPR and 1.206 NPR.

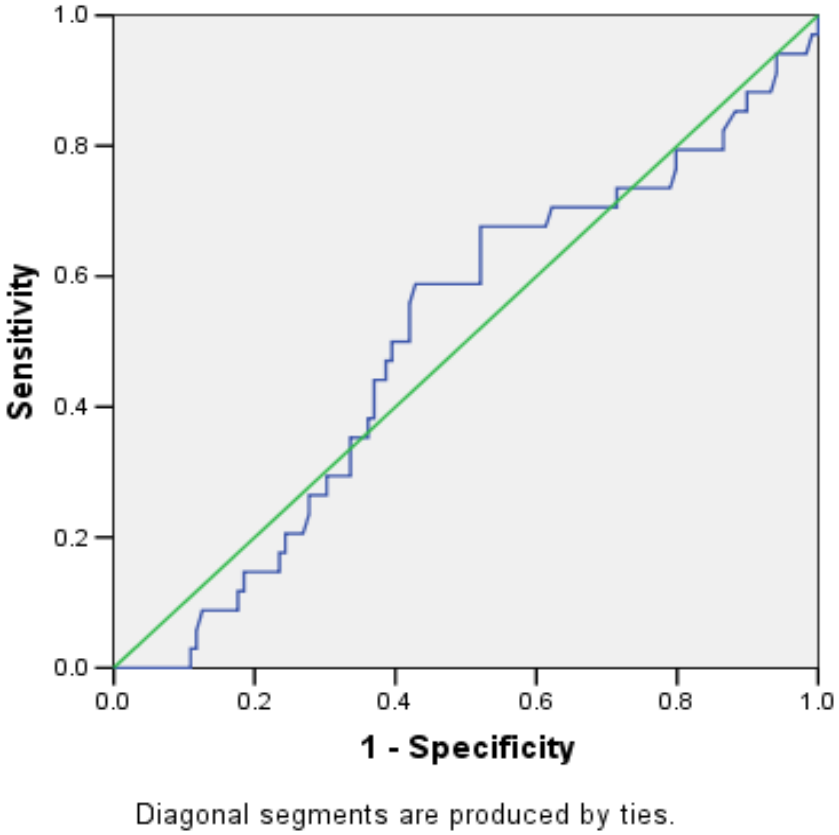

Figure 1. ROC curve of NLR examination results

Table 1. Characteristics of the study sample

Characteristics	PCR		p
	Positive n = 34	Negative n = 119	
Gender			
Male	19 (55.9%)	75 (63%)	
Female	15 (44.1%)	44 (37%)	0.450
Age			
0-5 years old	24 (70.6%)	94 (79%)	
6-18 years old	10 (29.4%)	25 (21%)	0.304
Symptoms			
Respiratory	21 (61.8%)	46 (38.7%)	
Non-respiratory	13 (38.2%)	73 (61.3%)	0.017
Rontgen			
Pneumonia	14 (41.2%)	13 (10.9%)	
Bronchopneumonia	13 (38.2%)	94 (79%)	<0.001
Bronchitis	(-)	2 (1.7%)	
Within normal limits	7 (11.1%)	10 (8.4%)	
Outcome			
Referred	2 (5.9%)	1 (0.8%)	
PICU transfer	9 (26.5%)	17 (14.3%)	<0.001
Self-isolation	16 (47.1%)	(-)	
Discarded	7 (20.6%)	101 (84.9%)	

Table 2. Determination results of the NLR cutoff for COVID-19 patients

Variable	AUC	Sensitivity	Specificity	Cutoff value	p
NLR	0.50	0.59	0.51	1.63	0.939

Table 3. Tabulation between NLR and PCR

NLR	PCR		Total n = 153
	Positive n = 34	Negative n = 119	
≥ 1.63	20	58	78
< 1.63	14	61	75

Table 4. The results of the diagnostic test

NLR	Diagnostic Test					
	Sensitivity	Specificity	PPV	NPV	PPR	NPR
1.63	58.8%	51.3%	0.26	0.81	1.21	0.80
3.13	26.5%	71.4%	0.21	0.77	0.97	1.21

DISCUSSION

The most research subjects with PCR (+)/- confirmed COVID-19 were male patients, there was 19 patients (55.9%), which is different from the study of Bourkhissi, et al. (2020) in which the study subjects were mostly women by 54%. The most age range with positive PCR was between 0-5 years old, which was 70.6%. This is in accordance with the research of Henry, et al. (2020) which states that the average COVID-19 in pediatrics is found in the range of 2 weeks - 7 years old. Meanwhile, in terms of symptoms, the majority were respiratory symptoms (fever, cold cough, shortness of breath, sore throat, anosmia, etc.) in 21 patients (61.8%), this is in line with research by Kai Qi, et al. (2021), in children with COVID-19 the symptoms that often appear are fever (48.5%), cough (40.6%), runny nose (11%), hard in breathing (7%) and sore throat (6.8%).

On chest X-ray examination/chest plain photo, there were 14 patients with pneumonia (41.2%), 13 patients with bronchopneumonia (38.2%) and 7 patients with normal results (11.1%). These results were in line with Serrano et al. (2020) who examined chest radiographs in pediatrics with COVID-19, the results were pneumonia (50%) and normal results (9.1%). X-rays of bronchopneumonia were also found in the study of López de Munain et al. (2021), there were 11 samples among the total 35 who were examined by plain chest radiographs in pediatric patients with COVID-19. Outcomes or patient outcomes in this study were obtained from electronic medical records and the results were different. There were 9 patients in PICU transferred care (26.5%) and 2 patients were referred (5.9%). Both of them have weak clinical symptoms, and breathing difficulties but no outcome is death.

This study found the cutoff value of NLR examination in pediatric patients was 1.625, with a sensitivity value of 0.59. This means that 58.8% of patients whose PCR is positive can be predicted with NLR >1.63. The specificity value was obtained at 0.51, which means that there was a 51.3% chance that negative PCR patients could be excluded whose NLR value was >1.63. While the PPV obtained is 0.26, it means that if the NLR result is >1.63, then there is a 25.6% chance that the PCR result will be positive. The NPV value was 0.81, so if the NLR result is <1.63, there is an 81.3% chance that the

patient will have a negative PCR result. The PPR obtained was 1.21, indicating that the ratio of patients with NLR >1.63 would have a positive PCR result 1.21 times greater than patients with NLR <1.63. The result of the NPR value was 0.80, which means that the probability ratio of patients with NLR <1.63 would have a positive PCR result 0.80 times less than patients with NLR results of > 1.63.

Meanwhile, compared to the cutoff limit value of 3.13, the analysis of the data in this study obtained a sensitivity of 26.5% and a specificity of 71.4%. The PPV value was 0.209, the NPV is 0.77, the PPR was 0.926 and the NPR value was 1.03. With these results, the NLR cutoff limit of 3.13 is also not an ideal value to be used as a predictor of COVID-19 diagnosis in pediatrics.

The results of the AUC/area under the ROC curve in this study were <0.7 i.e. 0.504, this caused the NLR value to not be used as a predictor of COVID-19 diagnosis in pediatric patients. The limitation of this study was that in determining the cutoff point, the number of samples was considered less so it took more to represent the population. In addition, the limited time of the study resulted in not all variables that could be studied further regarding COVID-19 in pediatrics.

The NLR cutoff value of 1,625 cannot be used as a predictor of COVID-19 diagnosis in pediatric patients at Dr. Oen Kandang Sapi Solo, Surakarta. In diagnosing COVID-19, it is necessary to look at various aspects such as anamnesis, related symptoms, other supporting examinations and of course with a standard reference examination, the RT-PCR Swab.

AUTHOR CONTRIBUTION

Dyah Wulaningsih Retno Edi and Irfan Dzakir Nugroho collected the data, did data analysis and wrote the manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest in this study.

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