



Comparison of Leukocyte, Neutrophil, and Lymphocyte Levels in Child Patients that Experienced Breathlessness with COVID-19 and Non-COVID-19 (2020–2021) in Medan, Indonesia

Hendri Wijaya^{1,2*} , Ayodhia Pitaloka^{1,2} , Rina Amelia³ , Ivnke Lubis¹ 

¹Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia; ²Adam Malik General Hospital, Medan, North Sumatera, Indonesia; ³Department of Community Medicine and Public Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia

Abstract

BACKGROUND: COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus-2. Various risk factors affect the morbidity and mortality of COVID-19, such as age, gender, ethnicity, comorbid conditions, and laboratory parameters. Clinical manifestations of COVID-19 in children are asymptomatic mild degrees or with acute upper respiratory tract symptoms and moderate degrees with clinical pneumonia. In the course of the COVID-19 pandemic, several biomarkers are needed that can be useful in risk stratification to predict the severity and fatality of COVID-19. Several biomarkers are used as markers of disease progression to a critical degree, such as leukocytes, lymphocytes, platelets, interleukin-6, and serum ferritin. Increased leukocytes and neutrophils and decreased lymphocytes are associated with severity and mortality in COVID-19. Laboratory findings in children with COVID-19 include decreased lymphocytes, leukopenia, and increased procalcitonin. In severe COVID-19, children often have abnormal laboratory parameters that suggest a systemic inflammatory response.

AIM: This study aims to compare leukocytes, neutrophils, and lymphocytes levels in children with the complaints of shortness of breath with COVID-19 and non-COVID-19 pediatric patients.

MATERIALS AND METHODS: This study is an analytic study with a cross-sectional approach to pediatric patients treated in Haji Adam Malik General Hospital Medan with the complaints of shortness of breath. Patient data were assessed based on the characteristic values of hemoglobin, leukocytes, neutrophils, lymphocytes, and COVID-19 polymerase chain reaction results and then analyzed using SPSS for Windows software. The study samples were 276 patients, with 43 confirmed positive COVID-19 patients and 233 negative patients. The source of this research data is data from the patient's medical record for 1 year (2020–2021).

RESULTS: The statistical analysis results found differences in the levels of leukocytes, neutrophils, and lymphocytes in children diagnosed with COVID-19 and non-COVID-19 ($p < 0.05$). However, there was no difference in hemoglobin levels in children who were congested with COVID-19 and non-COVID-19 ($p > 0.05$).

CONCLUSION: These results are consistent with several cases and previous studies where the levels of leukocytes, neutrophils, and lymphocytes can be used as a detection tool and a diagnostic and prognostic tool in COVID-19 patients

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***Correspondence:** Hendri Wijaya, Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia. E-mail: hendri.wijaya@usu.ac.id
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Introduction

COVID-19 is a zoonotic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Transmission of COVID-19 from person to person occurs through the spread of droplets when an infected person coughs or sneezes [2]. Various risk factors affect the morbidity and mortality of COVID-19, such as age, gender, ethnicity, comorbid conditions, and laboratory parameters. Individuals who are older and with comorbid conditions have a higher risk of COVID-19 mortality. However, younger individuals without underlying disease may also develop fatal complications such as myocarditis and the development of disseminated intravascular coagulopathy [3]. COVID-19 from person to person

occurs through the spread of droplets when an infected person coughs or sneezes [2]. In a study in seven countries, namely, the United States, Britain, Italy, Germany, Spain, France, and South Korea, the child mortality rate due to COVID-19 until February 2021 was still rare at 0.71/100,000 population [4].

The clinical manifestations of COVID-19 in children are asymptomatic mild degrees or with acute upper respiratory tract symptoms and moderate degrees with clinical pneumonia [5]. In general, the symptoms of COVID-19 in children are mild and can be treated at home. However, children with moderate or severe symptoms require hospitalization for observation and supportive care [6]. COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis [7]. In the course of the COVID-19 pandemic, several biomarkers are needed that can be

useful in risk stratification to predict the severity and fatality of COVID-19. Several biomarkers are used as markers of disease progression to a critical degree, such as leukocytes, lymphocytes, platelets, interleukin (IL)-6, and serum ferritin [8].

An increase in leukocytes and neutrophils and a decrease in lymphocytes are associated with the severity and mortality of COVID-19 [8]. Lymphopenia can be considered a cardinal laboratory finding with prognostic potential. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio can be of prognostic value in determining severe cases of COVID-19 [7]. Laboratory findings in children with COVID-19 include decreased lymphocytes, leukopenia, and increased procalcitonin [5]. In severe COVID-19, children often have abnormal laboratory parameters that suggest a systemic inflammatory response. Severe COVID-19 is often complicated by leukopenia, lymphopenia, thrombocytopenia, and coagulopathy, leading to disseminated intravascular coagulopathy [7]. Therefore, in this study, routine blood tests were carried out, including the levels of leukocytes, neutrophils, and lymphocytes in children with COVID-19 and non-COVID-19. This study aims to compare the levels of leukocytes, neutrophils, and lymphocytes in children who are congested with COVID-19 and non-COVID-19 sufferers.

Materials and Methods

This study is an analytic study with a cross-sectional approach to pediatric patients who were treated in Haji Adam Malik Hospital Medan with the complaints of shortness of breath. Patient data were assessed based on the characteristic values of hemoglobin, leukocytes, neutrophils, lymphocytes, and COVID-19 polymerase chain reaction (PCR) results, and then, statistical analysis was performed using SPSS software on a computer. The pediatric patient was then checked for COVID-19 status using a PCR swab, and then, routine blood tests were carried out. The study samples were 276 patients, with 43 confirmed positive COVID-19 patients and the remaining 233 negative patients. The source of this research data is from the patient's medical record for 1 year (2020–2021).

Univariate analysis was performed to obtain the distribution of sample characteristics. Categorical data will be displayed as frequency and percentage, while numerical data as mean and standard deviation if normally distributed or as median and minimum and maximum values if data are not normally distributed. The data on the characteristics of the patients were then tested for the normality of the data distribution using the Kolmogorov–Smirnov. Furthermore, the data were analyzed using the independent t-test analysis test if the data were normally distributed ($p < 0.05$) or

the Mann–Whitney statistical test was used if the data were not normally distributed ($p < 0.05$) [9].

Results

All participants who took part in this study were 276 people and were assessed based on characteristics including the values of hemoglobin, leukocytes, neutrophils, lymphocytes, and COVID-19 PCR results. Based on the hemoglobin value, the highest percentage was 40.6% (112 people) with a hemoglobin value <12 g/dL followed by a hemoglobin value of 15–16 g/dL with a percentage of 12.3% (34 people). Only 3.6% (10 people) had a hemoglobin value of 17–18 g/dL. From the leukocyte value, most of the participants had a leukocyte value above 11,000 L, which was 69.2% (191 people), but only about 5.4% (15 people) had a leukocyte value <4000 L. As many as, 60.1% (166 people) had neutrophil values above 60% for neutrophil values. The values obtained from the lymphocyte examination were the highest, namely, 43.8% (121 people) with $<20\%$ lymphocytes, 38.8% (107 people) with 20–40% lymphocytes, and the lowest was 17.4% (48 people) with $>40\%$ lymphocytes. From the COVID-19 PCR examination, participants with positive results were 15.6% (43 people) and 84.4% (233 people) negative. Patient characteristics are shown in Table 1.

Table 1: Characteristics of patients based on levels of hemoglobin, leukocytes, neutrophils, lymphocytes, and PCR results

Characteristics	Frequency (n)	Percentage
Hemoglobin (g/dL)		
<12	112	40.6
12–13	32	11.6
13–14	32	11.6
14–15	23	8.3
15–16	34	12.3
16–17	20	7.2
17–18	10	3.6
>18	13	4.7
Leukocytes (μ L)		
<4,000	15	5.4
4,000–11,000	70	25.4
>11,000	191	69.2
Neutrophils (%)		
<40	45	16.3
40–60	65	23.6
>60	166	60.1
Lymphocytes (%)		
<20	121	43.8
20–40	107	38.8
>40	48	17.4
PCR COVID-19		
Positive	43	15.6
Negative	233	84.4

PCR: Polymerase chain reaction.

The results of the analysis of descriptive statistical values from the examination of hemoglobin, leukocytes, neutrophils, and lymphocytes are shown in Table 2. From the statistical analysis results, it was found that the average hemoglobin value was 12.43 ± 3.69 g/dL with a median of 12.80 g/dL. Meanwhile, from the results of leukocyte examination, the average value was 25,695.43, and the median was 15.59. The average neutrophil and

lymphocyte examination value was $59.67 \pm 21.38\%$ and $26.14 \pm 16.55\%$, while the median value was 65.50 for neutrophils and 22.15 for lymphocytes. Table 3 showed the results of the analysis using the Mann–Whitney test, it was found that there were differences in the levels of leukocytes, neutrophils, and lymphocytes in children who were congested with COVID-19 and non-COVID-19 ($p < 0.05$). However, there was no difference in hemoglobin levels in children who were congested with COVID-19 and non-COVID-19 ($p > 0.05$).

Table 2: Levels of hemoglobin, leukocytes, neutrophils, and lymphocytes in children who are congested with COVID-19 and non-COVID-19

Parameter	Mean	Median	SD	Min	Max
Hemoglobin (g/dL)	12.43	12.80	3.69	0.30	20.0
Leukocytes (μ L)	25,695.43	15.59	67,864	1470	743,680
Neutrophils (%)	59.67	65.50	21.38	0.70	95.0
Lymphocytes (%)	26.14	22.15	16.55	0.30	91.10

Discussion

In this cross-sectional study, it was found that there were significant differences between the levels of leukocytes, neutrophils, and lymphocytes in routine blood examinations between pediatric patients complaining of shortness of breath with confirmed COVID-19 and non-COVID-19 taken in the 2020–2021 period at the HAMGH Medan. The results are consistent with several previous studies. A study by Wagner found that routine blood tests can be used to help diagnose diseases such as acute kidney injury (AKI) with signs such as lymphopenia and help in the prognosis of diseases such as COVID-19 [10]. In a study by Fuad *et al.* on patients in a Respiratory Intensive Care Unit in a hospital in the city of Banda Aceh from March to September 2020, it was found that COVID-19 patients change in neutrophil and lymphocyte levels can be used to determine the probability of mortality and morbidity. In COVID-19 patients where 16.6% had high levels of neutrophils and lymphocytes, it was recognized that further research was needed to examine at-risk demographics and COVID-19 19 such as diabetes, hypertension, and obesity to strengthen the findings of this study [11].

For pediatric patients themselves, in a study in 2020, in a study in China, it was found that among 182 pediatric patients in the study, levels of neutrophils, lymphocytes, and leukocytes did not have a significant relationship in COVID-19 when compared with adult patients. In addition, pediatric patients who present with COVID-19 will usually not complain of severe symptoms or may be asymptomatic. Further studies should be conducted with larger sample sizes in which patients with allergies and other respiratory disorders are given more attention [12].

Results from the previous research studies provide deep insight into immunological effects in

Table 3: Comparison of hemoglobin, neutrophil, and lymphocyte levels in congested children with COVID-19 and non-COVID-19

Variable	non COVID-19 (n = 233)	COVID-19 (n = 43)	p-value
Hemoglobin (Hb) (mean; median; SD)	12.5; 12.6; 3.7	11.9; 13.0; 3.6	0.269
Leukocytes	24,298.9; 16,820.0; 59,008.3	33,263.0; 9,640.0; 104,096.2	0.0001*
Neutrophils	61.0; 67.8; 20.9	52.4; 55.7; 22.6	0.007*
Lymphocytes	24.8; 20.9; 15.5	33.6; 32.3; 20.1	0.004*

children with COVID-19. Older children had more changes in lymphocyte subsets, including more cases with increased T-cell and CD8+ T-cell percentages and decreased B-cell counts. Younger children were more likely to be associated with increased cell counts and percentages. Consistent with clinical symptoms and laboratory findings, subsets of lymphocytes and cytokines did not differ in allergic and non-allergic COVID-19 patients. Thus, allergy plays a more significant and often overlooked role in the incidence, course, and outcome of COVID-19 in children [12].

A study conducted in China found no difference between severe and moderate cases in leukocyte count in correlation analysis, and lymphopenia was reported to occur even when the leukocyte count was average. Consistent with the previous studies, lymphopenia was frequently detected even when leukocyte and neutrophil counts were average in the hospital setting for COVID-19 cases. Immune cells infiltrate the lungs and cause severe, unexplained lung infections.

In one study, the lymphocyte count was found to be $<1.0 \times 10^9/L$. The human immune response created by lymphocytes is triggered by a viral infection, whereas systemic infection suppresses cellular immunity. Novel coronavirus can mainly act on lymphocytes, especially T23 lymphocytes. Total lymphocytes, CD4+, T cells, CD8+ T cells, B cells, and NK cells were decreased in COVID-19 patients, and severe cases had lower levels of these cells than mild cases. Therefore, when induced by SARS-CoV-2 infection, inflammation-associated lymphopenia increases [13]. Studies show that when patients have no exclusive symptoms in the early stages of COVID-19 disease, the peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced. At the same time, these indicators may change as the disease progresses. A study in hospitalized patients diagnosed with COVID-19 based on a computed tomography scan showed that the leukocyte count was within normal limits in 68.1% of patients, increased in 12.3% of patients, and decreased in 19.6% of patients. Leukopenia has been reported in other studies as a possible association between the severity of leukopenia and the severity of COVID-19 [14].

According to Zhao *et al.*, COVID-19 cases with increased leukocyte counts showed increased concentrations of procalcitonin, C-reactive protein (CRP), and IL-6 in serum compared to patients with non-increased leukocyte counts. Thus, the study demonstrated that confirmed COVID-19 patients with elevated leukocyte counts had significantly higher rates of

a systemic inflammatory response, which was at least in part associated with critical illness progression, with high intensive care unit admission rates and high mortality. The study found that the levels of leukocyte and neutrophil count in the blood when counted, serum concentrations of CRP and IL-6 were significantly increased in patients with increased leukocyte counts with underlying chronic disease, compared with patients with elevated leukocyte counts without the chronic disease [15].

Patients with COVID-19 may have normal leukocyte counts or even low or high leukocyte counts. Further research on the relationship between leukocytes and COVID-19 could assist in following the progression of the disease and assist in making decisions about treatment strategies. The possibility of a cytokine storm alone should be avoided, and the use of granulocyte colony-stimulating factor for leukopenia associated with SARS-CoV-2 should be avoided as it may exacerbate conditions with the early development of acute respiratory distress syndrome [16].

Conclusion

There are significant differences in the levels of leukocytes, neutrophils, and lymphocytes in patients with shortness of breath with COVID-19 and patients complaining of shortness of breath without COVID-19. These results are consistent with several cases and previous studies where the levels of leukocytes, neutrophils, and lymphocytes can be used as a detection tool and a diagnostic and prognostic tool in COVID-19 patients. Further research is needed to determine how to use the measurement of leukocytes, neutrophils, and lymphocytes as a diagnostic tool and to assist in determining the prognosis.

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