

Correlation between Clinical and Laboratory Manifestation to The Severity and Outcome of COVID-19 Infection in Children with Cancer at RSUD Dr. Soetomo

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Abstract

COVID-19 infection in children is generally asymptomatic or with symptoms but milder than in adults, although symptoms of severe infection and death may also occur. Cancer patients have a high level of immunosuppression due to the anticancer therapy they are undergoing so that COVID-19 infection is more susceptible to complications. However, until now there have not been many reported cases of COVID-19 in pediatric patients with cancer, so it is not yet known whether there is a relationship between clinical and laboratory manifestations on the degree of severity and patient outcome. This study is an analytic observational study using a retrospective design, based on secondary data. Sampling was done by total sampling technique. Relationship analysis is used to answer the research hypothesis. To find out the relationship between variables, a chi-square and Fisher's exact test was used because the data taken was nominal. Based on the inclusion and exclusion criteria, a total of 36 samples were found to fulfill. The most age range in patients was 3-5 years (36.11%) and was dominated by male sex (63.88%). From 36 samples, 21 of them had blood cancer, with the most type being ALL (90.47%). The degree of severity with the highest rate was moderate (37.83%) and most of the patient outcomes were alive (75%). The analysis carried out stated that there was no relationship between clinical manifestations and the severity of the patient. However, a relationship was found between shortness of breath symptoms and patient outcomes. Meanwhile, in laboratory manifestations there was no relationship between the degree of severity and the patient's outcome. In conclusion, there is a relationship between symptoms of shortness of breath and the outcome of pediatric cancer patients with COVID-19 infection.

Keywords: COVID-19; childhood cancer; clinical manifestation; laboratory manifestation

1. Introduction

Coronavirus disease 2019 (COVID-19) has become a global concern since it was declared a pandemic by WHO in mid-2020. Since being identified, cases of COVID-19 have continued to increase significantly, both in children and adults. Compared to adults, the risk of infection with COVID-19 in

children is lower. However, risk factors related to severe infections need to be watched out for in children with comorbidities such as complex congenital conditions, obesity, diabetes, and cancer.¹ Recent studies have shown a link between cancer and an increased risk of developing COVID-19 infection into severe symptoms, even death.² High immunosuppression due to anticancer therapy being undertaken is one of the main reasons that lead to susceptibility in cancer patients. Especially in pediatric patients, persistent immune deficits after stopping chemotherapy can last up to 6-12 months.³ In addition to the presence of comorbidities, common symptoms in COVID-19 patients such as fever, cough and shortness of breath are often associated with an increased risk of the severity of the infection they suffer. Also, laboratory findings such as decreased lymphocytes are also often found in patients with severe infections.⁴

A study conducted by Zhu et al., 2021 shows that there is a relationship between the number of white blood cells and the death of cancer patients with COVID-19 infection.⁵ Meanwhile, Jaafarabadi et al., 2021 found an increase of up to 22 times the risk of severe COVID-19 in patients with anemia.⁶ Furthermore, related to clinical manifestations, a study in Brazil stated that there was a relationship between the presence of shortness of breath and comorbid symptoms and the risk of death from COVID-19.⁷ Xie et al., 2020 in their research also suggested a relationship between symptoms of shortness of breath and patient mortality.⁸

Although there have been previous studies regarding the relationship between clinical and laboratory manifestations on the degree of severity and outcome of COVID-19 patients, no specific studies have been conducted in pediatric patients in Indonesia. Therefore, researchers are interested in conducting research on children with cancer to find out whether there are differences in outcomes between adult patients and children. The aim of this study was to identify and analyze the relationship between clinical and laboratory features on the severity and outcome of COVID-19 infection in children with cancer.

2. Method

This research was an observational analytic study with a retrospective approach. Population of the samples are pediatric cancer patients aged 0-18 years who are infected with COVID-19 at Dr. Soetomo General Hospital Surabaya. The samples were collected by total sampling method, with total 36 patients. The dependent variables in this study were the degree of severity and patient outcomes. The independent variables included clinical manifestations (fever, cough, shortness of breath, digestive tract symptoms) and laboratory manifestations (lymphocyte count, erythrocyte count, Hb level, leukocyte count, platelet count). Statistical data were analyzed using the Chi-square test and Fisher's Exact in the SPSS application.

3. Results

Based on data obtained from April 2020-August 2021 at Dr. Soetomo General Hospital Surabaya, there are 46 pediatric cancer patients with COVID-19. Among the 46 patients, there are 6 patients who are not confirmed to have COVID-19. From the remaining 40 patients, 4 patients did not have complete blood count data so in the end there is only 36 patients who met the inclusion and exclusion criteria that could be analyzed.

Table 1. General characteristics of pediatric cancer patients with COVID-19

Category	N	%
Sex		
Male	23	63,88*
Female	13	36,12
Age		
1-2 years old	5	13,88
3-5 t years old	13	36,11*
6-11 years old	7	19,44
12-18 years old	11	30,55
Cancer Category		
Hematology		
ALL	19	90,47*
CML	2	9,53
Solid		
Mediastinal tumor	1	6,67
Suprasellar tumor	1	6,67
Retinoblastoma	1	6,67
Germinoma	1	6,67
Osteosarkoma	1	6,67
Melanoma	1	6,67
Lymphoma Hodgkin	1	6,67
Lymphoma Non Hodgkin	2	13,34
Nfroblastoma (Wilms tumor)	1	6,67
Glioma	1	6,67
Adrenal tumor	2	13,34
Sarcoma	1	6,67
Hepatic cancer	1	6,67
Outcome		
Life	27	75,00*
Death	9	25,00

*: variable with the highest frequency

In this study, characteristics were obtained in the form of gender, age, cancer category, degree of severity of COVID-19, and patient outcomes. The highest proportion of sex was male (59,55%) and the highest ighest age group is 3-5 years (32.43%). The distribution of cancer is divided into two categories, hematology and solid cancer, with 22 patients and 15 patients respectively. The cases of hematological cancer were dominated by ALL with 20 patients (90.90%). The degree of severity of COVID-19 in pediatric malignancy patients is divided into 5 categories, which is asymptomatic, mild, moderate, severe, and critical. The group with the highest number was the moderate category, namely 14 children (37.83%), while the lowest number was the severe category with 0 children (0.00%). Then for the distribution of patient outcomes, the results obtained were 28 living patients (75.67%) while 9 people died (24.33%).

Table 2. Subject characteristics and severity of COVID-19

Category	Non-severe N (%)	Severe N (%)
Sex		
Male	21 (58,33)*	2 (5,56)
Female	13 (36,11)	0
Age		
1-2 years old	5 (13,89)	0
3-5 years old	13 (36,11)*	0
6-11 years old	6 (16,67)	1 (2,78)
12-18 years old	10 (27,78)	1 (2,78)
Cancer Category		
Hematology		
ALL	18 (85,71)*	1 (4,76)
CML	2 (9,52)	0
Solid		
Mediastinal tumor	0	1 (6,67)
Suprasellar tumor	1 (6,67)	0
Retinoblastoma	1 (6,67)	0
Germinoma	1 (6,67)	0
Osteosarkoma	1 (6,67)	0
Melanoma	1 (6,67)	0
Lymphoma Hodgkin	1 (6,67)	0
Lymphoma Non Hodgkin	2 (13,34)	0
Nfibroblastoma (Wilms tumor)	1 (6,67)	0
Glioma	1 (6,67)	0
Adrenal tumor	2 (13,34)	0
Sarcoma	1 (6,67)	0
Hepatic cancer	1 (6,67)	0
Outcome		
Life	27 (75,00)*	0
Death	7 (19,44)	2 (5,56)

*: variable with the highest frequency

Based on the table above, patients in the severe category were only male (5.56%), and were included in the highest age group, namely 6-11 years (2.78%) and 12-18 years (2.78%). In the cancer category, the severe group had ALL (4.76%) and mediastinal tumor (6.67%). Furthermore, in patient outcomes, both severe patients were found to have died (5.56%).

Table 3. Clinical manifestations based on patient's degree of severity

Clinical Manifestations	Degree of Severity		OR	<i>p</i>	CI 95%	
	Non-severe (n=34)	Severe (n=2)			Lower	Upper
Fever			0,889	0,486	0,755	1,047
Yes	16	2				
No	18	0				
Cough			1,267	1,000	0,073	21,970
Yes	15	1				
No	19	1				
Dyspnea			0,867	0,167	0,711	1,057
Yes	13	2				
No	21	0				
Digestive tract symptoms			1,061	0,556	0,978	1,151
Yes	18	1				
No	16	1				

The table above shows that patients with non-severe severity have the most symptoms of fever. Meanwhile, in terms of severe severity, fever and shortness of breath have a similar number of cases. From the tests carried out, there was no relationship between clinical manifestations and the severity of the patient. This is evidenced by the results of the chi-square test which shows that all symptoms have a *p*-value > 0.05.

Table 4. Clinical manifestations based on patient outcomes

Clinical Manifestations	Outcome		OR	<i>p</i>	CI 95%	
	Life (n=27)	Death (n=9)			Lower	Upper
Fever			2,500	0,443	0,515	12,139
Yes	12	6				
No	15	3				
Cough			3,400	0,146	0,693	16,687
Yes	10	6				
No	17	3				
Dyspnea			8,313	0,019*	1,408	4,903
Yes	9	7				
No	18	2				
Digestive tract symptoms			1,346	1,000	1,108	1,636
Yes	16	6				
No	11	3				

*: significant value ($P < 0,05$)

Based on the data contained in the table above, it shows that the most common symptoms in patients who died were shortness of breath, followed by fever and cough. Meanwhile, in living patients, the most common symptom that patients have is fever. From the chi-square test conducted, a relationship between clinical manifestations and patient outcomes was found only in shortness of breath ($p < 0.05$). While the other symptoms had no relationship with the patient's outcome ($p > 0.05$).

Table 5. Laboratory manifestations based on degree of severity

Laboratory Manifestations	Degree of Severity		OR	<i>p</i>	CI 95%	
	Non-severe (n=34)	Severe (n=2)			Lower	Upper
Lymphocyte count*			1,125	0,486	0,955	1,325
Normal	16	2				
Low	7	0				
High	12	0				
Erythrocyte count			0,259	0,400	0,014	4,683
Normal	6	1				
Low	28	1				
Hb level			0,259	0,400	0,014	4,683
Normal	6	1				
Low	28	1				
Leukocyte count*			0,789	1,000	0,046	13,693
Normal	14	1				
Low	3	1				
High	18	0				
Thrombocyte count			1,111	0,492	0,960	1,286
Normal	18	2				
Low	15	0				
High	2	0				

*: using fisher's exact test

Based on the data written in the table, the results of laboratory tests that are most commonly found in non-severe patients are anemia. While in the degree of severe, there is no significant difference from the results of the examinations carried out. Furthermore, in the chi-square and Fisher's exact tests, it was found that the number of lymphocytes, the number of erythrocytes, the Hb level, the number of leukocytes, and the number of platelets were not related to the severity of the patient's COVID-19 ($p > 0.05$).

Table 6. Laboratory manifestations based on patient outcomes

Laboratory Manifestations	Degree of Severity		OR	<i>p</i>	CI 95%	
	Life (n=27)	Death (n=9)			Lower	Upper
Lymphocyte count*			0,743	1,000	0,163	3,383
Normal	13	5				
Low	4	3				
High	10	1				
Erythrocyte count			1,000	1,000	0,163	6,318
Normal	6	2				
Low	21	7				
Hb level			1,000	1,000	0,163	6,318
Normal	6	2				
Low	21	7				
Leukocyte count*			0,550	0,470	0,120	2,521
Normal	11	4				
Low	2	2				
High	14	3				
Thrombocyte count			0,265	0,245	0,046	1,517
Normal	13	7				
Low	12	2				
High	2	0				

*: using fisher's exact test

Based on the table, the most common laboratory results in both living and deceased patients are anemia or low erythrocyte counts and Hb levels. In the chi-square and fisher's exact tests that were carried out, it was found that there was no relationship between the results of laboratory tests and patient outcomes, as evidenced by the value of $p < 0.05$.

4. Discussion

In this study, it was found that there was no relationship between clinical manifestations and the severity of COVID-19 infection. However, there is a relationship between shortness of breath symptoms and patient outcomes. The same result was shown by Macedo et al. 2021 in his study in Brazil, that the clinical symptoms of shortness of breath and comorbidities in COVID-19 infection were associated with patient mortality.⁷ Another study conducted in China also showed a correlation between shortness of breath symptoms and patient death.⁸

Chen et al., 2020 in his research suggested that shortness of breath or dyspnea was the single risk factor for death in 74% of patients with severe degrees. An increased risk of mortality in patients with shortness of breath is associated with ARDS. Shortness of breath is one of the early clinical manifestations of ARDS, which can progressively develop into respiratory failure.⁹ According to Hernandez et al., 2021, shortness of breath in children is the most common respiratory syndrome occurring in more severe degrees of COVID-19 infection. This is what ultimately causes the death of COVID-19 patients.¹⁰ Another study reported that the incidence rate of ARDS reached 70% in pediatric patients with severe COVID-19 infection accompanied by comorbidities.¹¹

In a literature study relating ARDS frequency, ICU admission rates, and mortality among patients with COVID-19, it was found that approximately $\frac{1}{3}$ of them progressively developed ARDS, $\frac{1}{4}$ required transfer to ICU, and $\frac{1}{6}$ the remainder died. The incidence of ARDS in COVID-19 patients is 90% with a mortality rate of 45% in ARDS related to COVID-19. The high incidence rate of ARDS among COVID-19 patients was examined at postmortem examination and the main similarity was found, namely the presence of evenly distributed alveolar damage.¹²

Another study has shown a relationship between shortness of breath symptoms and the need for ventilators in patients. Annoni et al., 2021 stated in their research that COVID-19 patients with $\text{SpO}_2 < 90\%$ were associated with death outcomes. Patients with shortness of breath experience low oxygen saturation and need ventilation assistance, so it can be concluded that these two studies prove the association of symptoms of shortness of breath with the death of patients with COVID-19 infection. Most COVID-19 patients experience similar symptoms, and the causes of death are related to low oxygen saturation and respiratory problems in the lungs.¹³

Furthermore, from the analysis that has been carried out, in this study it was found that there was no relationship between the number of lymphocytes, the number of erythrocytes, the Hb level, the number of leukocytes, and the number of platelets on the degree of severity and outcome of pediatric cancer patients with COVID-19 infection. Research conducted in Wuhan, China showed no significant difference between an increase in the number of lymphocytes and the severity of pediatric patients.¹¹ In another meta-analysis study, it was found that there were no significant differences in laboratory results in children infected with COVID-19, although an increase in the number of leukocytes, lymphocytes, and platelets was found in children aged < 1 year.¹⁴

Soebandrio et al., 2021 in his research in Indonesia explained that there was no association between patients with leukopenia, lymphopenia, and thrombocytopenia to the severity of their symptoms ($p > 0.05$).¹⁵ Research conducted at the Singapore National Center for Infectious Disease (NCID) found that there was no significant difference in the results of laboratory tests in COVID-19 patients with persistent fever and saddleback fever, with an indication that patients with persistent fever had a higher level of severity and required treatment. ICU care compared to saddleback fever.¹⁶

In contrast to previous research, Jaafarabadi et al., 2021 in his research explained that COVID-19 patients with anemia are more susceptible to getting more severe infections.⁶ In line with this, revealed in a meta-analysis study, it was found that 63% of cases experienced a decrease in the number of lymphocytes, then the correlation test found a link between lymphopenia and the severity of COVID-19 infection.¹⁷ Another study conducted in America also revealed a relationship between the number of white blood cells and patient death.⁵ This difference in results can occur due to differences in the samples studied. In these three studies, the sample studied was adults and accompanied by non-cancer-specific comorbidities.

5. Conclusion and Suggestion

In this study it was found that there was a relationship between shortness of breath and outcomes in pediatric cancer patients with COVID-19 infection ($p < 0.05$; CI 95% 1,408-4,903). The limitation of this study is that data on clinical and laboratory manifestations were taken at the beginning of the COVID-19 infection without paying attention to changes during treatment, so that these results might affect the correlation with the degree of severity and patient outcome. Therefore, it is hoped that future research can use a prospective sampling method so that the data obtained can be more specific.

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References

1. Jiang, L., Tang, K., Levin, M., Irfan, O., Morris, S. K., Wilson, K., Klein, J. D., & Bhutta, Z. A. 2020, 'COVID-19 and multisystem inflammatory syndrome in children and adolescent'. *The Lancet. Infectious diseases*, vol 20, no 11, pp 276–288
2. Saini, K. S., Tagliamento, M., Lambertini, M., McNally, R., Romano, M., Leone, M., Curigliano, G., & de Azambuja, E., 2020, 'Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies', *European Journal of Cancer*, vol 139, pp 43-50.
3. Ruggiero, A., Romano, A., & Attinà, G., 2020, 'Facing the COVID-19 outbreak in children with cancer', *Drugs in context*, vol 9, pp 1-3.
4. Hazarika, M., Reddy, T. R., K Rai, A., S Roy, P., Iqbal, A., Barbhuiyan, S., Raj, N., Mallik, S., & Sarangi, S. S., 2022, 'COVID-19 prevalence and survival outcome in pediatric cancer patients undergoing chemotherapy: a study from tertiary cancer center of north-east india', *Asian Pacific Journal of Cancer Care*, vol 7, no 3, pp 475-480.
5. Zhu, B., Feng, X., & Jiang, C., 2021, 'Correlation between white blood cell count at admission and mortality in COVID-19 patients: a retrospective study', *BMC Infectious Disease*, vol 21, no 1, pp 574-579.
6. Jaafarabadi, M., Begheri, M., Shariat, M., Raeisic, K., Ranjbar, A., Ghafoori, F., & Haghollahi, F., 2021, 'The evaluation of clinical symptoms and underlying factors in infected patients with covid-19', *Tehran University Medical Journal*, vol 78, no 10, pp 668-677.

7. Macedo M. C. F, Pinheiro, I. M., Carvalho, C. J. L., Fraga, H. C. J. R., Araujo, I. P. C., Montes, S. S., Araujo, O. A. C., Alves, L. A., Saba, H., Araújo, M. L. V., Queiroz, I. T. L., Sampaio, R. L., Souza, M. S. P. L., da Silva, A. C. F. N., & Souza, A. C. S. (2020). 2021, 'Correlation between hospitalized patients' demographics, symptoms, comorbidities, and covid-19 pandemics in Bahia, Brazil', *Plos One*, vol 16, no 3, pp 1-15.
8. Xie, J., Covassin, N., Fan, Z., Singh, P., Gao, W., Li, G., Kara, T., & Somers, V. K., 2020, 'Association between hypoxemia and mortality in patients with covid-19', *Mayo Clinic Proceedings*, vol 95, no 6, pp 1138-1147.
9. Chen, Z., Xiong, H., Li, J. X., Li, H., Tao, F., Yang, Y. T., Wu, B., Tang, W., Teng, J. X., Fu, Q., & Yang, L., 2020, 'COVID-19 with post-chemotherapy agranulocytosis in childhood acute leukemia: a case report', *Zhonghua Xue Ye Xue Za Zhi*, vol 41, no 4, pp 341-343.
10. Hernandez, J., & Orozco, I., 2021, 'COVID-19 in children: respiratory involvement and some differences with the adults', *Pediatric Pulmonology*, vol 9, pp 1-9.
11. Wang, Y., Zhu, F., Wang, C., Wu, J., Liu, J., Chen, X., Xiao, H., Liu, Z., Wu, Z., Lu, X., Ma, J., Zeng, Y., Peng, H., & Sun, D., 2020, 'Children hospitalized with severe COVID-19 in Wuhan', *The Pediatrics Infectious Disease Journal*, vol 39, no 7, pp 91-94.
12. Tzotzos, S. J, Fischer, B., Fischer, H., & Zeitlinger, M., 2020, "Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey", *Critical Care*, vol 24, no 1, pp 516-520.
13. Annoni, A. D., Conte, E., & Mancini, M. E., 2021, 'Quantitative evaluation of covid-19 pneumonia lung extension by specific software and correlation with patient outcome'. *Diagnostics*. Vol 11, no 2, pp 265-276.
14. Henry, B. M, Benoit, S. W., de Oliveira, M. H. S., Hsieh, W. C., Benoit, J., Ballout, R. A., Plebani, M., & Lippi, G. 2020, 'Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): a pooled analysis and review', *Clinical Biochemistry*, vol 81, pp 1-8.
15. Soebandrio, A., Kusumaningrum, T., Yudhaputri, F. A., Oktavianthi, S., Malik, S. G., & Myint, K. S. E., 2021, 'Characteristics of children with confirmed SARS-CoV-2 infection in Indonesia', *Journal of Clinical Virology Plus*, vol 1, no 3, pp 1-5.
16. Ng, D. H. L., Choy, C. Y., Chan, Y. H., Young, B. E., Fong, S. W., Ng, L. F. P., Renia, L., Lye, D. C., Chia, P. Y., & National Centre for Infectious Diseases COVID-19 Outbreak Research Team, 2020, 'Fever patterns, cytokine profiles, and outcomes in COVID-19', *Open Forum Infectious Diseases*, vol 7, no 9, pp 1-7.
17. Goudouris, E.S., 2021, 'Laboratory diagnosis of COVID-19', *Jornal de pediatria*, vol 97, no 1, pp 7-12.