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RESEARCH ARTICLE **OPEN ACCESS**

Comparison of Changes in the Neutrophil-lymphocyte Ratio (NLR) and Post-surgery Outcomes in Child Patients with COVID-19 and Non-COVID-19

Rusmin B. Syukur[1,2,*], Arie Utariani[1], Muh R. Achmad[2], Lucky Andriyanto[1], Ezra Octaliansah[3], Windhu Purnomo[4] and Mahendratama P. Adhi[5]

[1]*Department of Anesthesiology and Reanimation, Faculty of Medicine, Airlangga University / Dr. Sutomo Hospital, Surabaya, East Java, Indonesia*
[2]*Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Hasanuddin University / Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia*
[3]*Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Padjadjaran University / Dr Hasan Sadikin National Referral Hospital, Bandung, West Java, Indonesia*
[4]*Department of Epidemiology, Population Biostatistics and Health Promotion Faculty of Public Health, Airlangga University, Surabaya, East Java, Indonesia*
[5]*Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Lambung Mangkurat University / Ulin Hospital, Banjarmasin, Indonesia*

Abstract:

Background: Pediatric patients with COVID-19 who undergo surgery have two actual problems, both the presence of a viral inflammatory response and an inflammatory response to surgery, which can affect the outcome of surgery and therapy. NLR is considered a fairly accurate predictor of surgery and COVID-19 infection.

Objective: This study aims to investigate the effect of changes in neutrophil-lymphocyte (NLR) on post-surgery outcomes in pediatric patients with COVID-19 infection.

Methods: It is a retrospective cohort study with an observational analysis. This research is a multi-center study on COVID-19 patients using a data bank of pediatric patients with COVID-19 and control patients non COVID-19 children undergoing surgery in three hospitals. Data recorded were age, gender, nutritional status, anesthetic status before surgery, length of stay, repeat surgery, sepsis, septic shock, and mortality. Statistical analysis was performed by the U-mann Whitney test.

Results: The study sample consisted of 87 total samples consisting of 2 groups, namely the group of pediatric patients with 29 samples with COVID-19 and 58 non-COVID-19 samples. Gender, nutritional status, length of stay, the incidence of reoperation, sepsis, septic shock, and mortality were not significantly different between the two groups with a $p<0.05$. Risk analysis by looking at the incidence of sepsis and septic shock obtained an intersection point of 2.175 and 2.225, respectively. Analysis of changes in the NLR (delta-NLR) in the mortality events of the COVID-19 group and non-COVID-19 found that the NLR of the COVID-19 group was two times greater than the cut-off NLR of 2,175.

Conclusion: There is no difference in the outcome of surgery for children with COVID-19 and non-COVID-19 based on the NLR change analysis.

Keywords: NLR, Pediatric anesthesia, Pediatric surgery, COVID-19, Mortality, Perioperative.

*Address correspondence to this author at the Department of Anesthesiology and Reanimation, Faculty of Medicine, Airlangga University / Dr. Sutomo Hospital, Surabaya, East Java, Indonesia; Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Hasanuddin University / Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia; E-mails: rusminsyukur@unhas.ac.id, cummink7120@gmail.com

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1. INTRODUCTION

COVID-19 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that can affect all ages, ranging from infants and children to the elderly [1]. COVID-19, which affects children, generally has mild or moderate clinical symptoms and rarely manifests severely compared to adults. Cui *et al.* (2020) in China found that of 2597 cases of COVID-19 children, 7.6% were asymptomatic, and 45.5% were mild [2]. The Indonesian Pediatric Association (IDAI) found COVID-19 cases that must undergo surgery in the child population are 11.3%. Children who undergo surgery, in addition to stress due to COVID-19 infection, also get an additional stress response in the form of anesthesia and surgery. This situation can cause complex metabolic, hormonal, hematological, and immunological responses and activate the sympathetic nervous system, which is generally referred to as a stress response [3].

One examination that can measure the stress response to surgery easily and flexibly is the neutrophil-lymphocyte ratio, which is an inflammatory marker reported to have a good prognostic value and diagnose an acute condition or predict mortality or morbidity [4, 5]. Hajibandeh S *et al.* (2019) found significant results that NLR can predict the diagnosis and evaluation of appendicitis severity [6-8]. Djordjevic *et al.* (2018) found significantly high NLR with mortality in inflammatory cases with or without infection in two groups of survivors and nonsurvivors [8, 9].

Neutrophil and lymphocyte inflammatory biomarker changes have high prognostic value in pediatric patients with COVID-19, but increased NLR only occurs in severe infections [10-13]. The NLR will provide a meaningful prognostic value if there is a difference in the NLR examination with periodic NLR every day, especially if there is an increase in peak in NLR. Jimeno S *et al.* (2020) found that the NLR as an inflammatory marker for endothelial dysfunction can assess progressivity toward worsening in COVID-19 patients [14].

Pediatric patients with COVID-19 who undergo surgery have two actual problems, namely the presence of a viral inflammatory response and a surgical inflammatory response that can affect the outcome. Based on several studies that use hematological examinations of neutrophils, lymphocytes, and NLR as a fairly accurate predictor tool in surgery and COVID-19 infection, the use of NLR in assessing postoperative outcomes has never been studied in COVID-19 children.

This study aims to analyse the effect of changes in NLR in pediatric patients with COVID-19 and non-COVID-19 undergoing surgery on the incidence of reoperation, length of stay, incidence of sepsis, septic shock, and mortality rates.

2. METHODS

This study used an analytic *case-control study* design to determine the effect of changes in NLR on the incidence of outcomes in pediatric patients with COVID-19 and non COVID-19 group who underwent surgery. Data were collected from the medical records of pediatric patients aged <18 years with COVID-19 infection and non-COVID-19 who underwent semergency surgery at Dr. Wahidin Sudirohusodo Hospital Makassar, Dr. Soetomo Hospital Surabaya, and Ulin Hospital Banjarmasin in the period from April, 2020 to December, 2021. The total sample was 29 patients with COVID-19 and 58 patients in non-COVID-19 group as a control.

Patients diagnosed with COVID-19 in this study were patients who underwent emergency surgery, which was confirmed by positive COVID-19 RT-PCR examination results. Nasopharyngeal swab specimen collection was carried out before surgery. Most of the examination results were only obtained after the operation was complete. This was due to emergency reasons and limited resources. The patient underwent emergency surgery immediately, less than 6 hours after it was planned.

The laboratory parameters used were neutrophil and lymphocyte used to calculate the neutrophil-lymphocyte ratio (NLR) before and after surgery, as well as changes in NLR. The neutrophil-lymphocyte ratio was measured within ≤ 24 hours before and after surgery.

In addition, data on gender, age, nutritional status, physical status (ASA PS), incidence of reoperation, sepsis, septic shock, and mortality were recorded.

Statistical analysis was carried out using the IBM SPSS Statistics Program. Univariate analysis was performed to examine the basic characteristics of the study sample, then continued with the chi-square test to investigate the relationship and the Wilcoxon test to examine the comparison of NLR before and after surgery in each group. The Mann-Whitney test was used to examine the comparison between the COVID-19 and non-COVID-19 groups if the data was not normally distributed, and the unpaired t-test if the data was normally distributed.

3. RESULTS

The study sample consisted of 87 total samples consisting of 2 groups, namely the group of pediatric patients with COVID-19, as many as 29 samples and non-COVID-19, as many as 58 samples. The characteristics of the study samples are presented in Table **1**. The variables presented were gender, age group, physical status (ASA PS), re-surgery, sepsis, septic shock, and mortality for both groups.

Table **2** presents the statistical analysis of the comparison of NLR before and after surgery in pediatric patients with COVID-19 and non-COVID-19. The results of the analysis showed that there was no significant difference between the NLR before and after surgery in both groups, and the significance in the COVID-19 group was 0.086, and in the non-COVID-19 group, it was 0.721. The comparison of NLR before surgery and after surgery, changes in NLR, and length of stay in pediatric patients with COVID-19 and non-COVID-19 groups was made. The results of the analysis showed that there was a difference in median NLR between pediatric patients with COVID-19

and the non-COVID-19 group, where the median NLR before surgery was higher at 5.16 compared to after surgery at 4.28, and the change in NLR was 0.64 in pediatric patients with COVID-19 compared to non COVID-19 group. However, there was no statistically significant difference ($p > 0.05$). For the length of stay, there was no significant difference in both groups ($p > 0.05$).

Table 3 presents a statistical analysis of differences in NLR and changes in NLR towards reoperation in both groups. The results of the analysis showed that there was no significant difference between changes in NLR and the incidence of reoperation in both groups, with a significance value in the COVID-19 group of 0.513 and non-COVID-19 group of 0.606.

Table 4 presents a statistical analysis of differences in NLR and changes in NLR on the incidence of sepsis in pediatric patients both with and without COVID-19. The results of the analysis showed that there was no significant difference between changes in NLR and the incidence of sepsis in the two sample groups, with a significance value in the COVID-19 group of 0.817 and non-COVID-19 group of 0.978.

Table 5 presents a statistical analysis of differences in NLR and changes in NLR on the incidence of septic shock in pediatric patients both with and without COVID-19. The results of the analysis showed that there was no significant difference between changes in NLR and the incidence of septic shock in the two sample groups, with a significance value in the COVID-19 group of 0.392 and non-COVID-19 group of 0.527.

Table 1. Characteristics samples.

Characteristics	COVID-19		Non COVID-19		*P-value*
	N = 29	%	N = 58	%	
Gender	-	-	-	-	-
Male	20	69%	39	67%	0,871
Women	9	31%	19	33%	
Age Group	-	-	-	-	-
Neonates	5	17%	9	16%	0,716
Baby	6	21%	11	19%	
Children	8	28%	23	40%	
Teenagers	10	34%	15	26%	
Nutritional Status	-	-	-	-	-
Malnutrition	4	14%	7	12%	0,986
Undernourished	4	14%	10	17%	
Good Nutrition	19	66%	36	62%	
More Nutrition	1	3%	2	3%	
Obesity	1	3%	3	5%	
Physical Status (ASA PS)	-	-	-	-	-
Class 2	23	79%	42	72%	0,485
Class 3	6	21%	16	28%	
Operation	-	-	-	-	-
Exploratory Laparotomy	9	31%	20	34%	-
Craniectomy Evacuation of Hematoma	5	17%	9	16%	-
Colostomy	2	7%	3	5%	-
Appendectomy	1	3%	3	5%	-
Open Reduction Internal Fixation	1	3%	3	5%	-
Miscellaneous	11	40%	20	34%	-
Re-surgery	-	-	-	-	-
Yes	5	17%	10	17%	> 0,05
No	24	83%	48	83%	
Sepsis	-	-	-	-	-
Yes	4	14%	16	28%	0,149
No	25	86%	42	72%	
Septic Shock	-	-	-	-	-
Yes	4	14%	6	10%	0,635
No	25	86%	52	90%	
Mortality	-	-	-	-	-
Yes	5	17%	14	24%	0,463
No	24	83%	44	76%	
Total	29	100%	58	100%	

Table 2. Comparison of pre-surgery and post-surgery NLR, changes in NLR, and length of stay in pediatric patients with COVID-19 and non-COVID-19.

Variables	COVID-19 [Median (Min-Max)]	Non COVID-19 [Median (Min-Max)]	*P*
NLR Before Surgery	5.16 (0,18 - 34,61)a	3.75 (0,20 - 24,51)b	0,971
NLR After Surgery	4.28 (0,15 - 40,18)a	3.64 (0,26 - 32,59)b	0,725
Change in NLR	0,64 (-8,28 - 18,07)	0,05 (-17,42 - 28,80)	0,152
Length of Hospitalization	11.62 ± 6,85	15,03 ± 12,48	0,412

Note: a Comparison between NLR before and after surgery in the COVID-19 group ($p = 0.086$).
b Comparison between NLR before and after surgery in the non-COVID-19 group ($p = 0.721$).

Table 3. Differences in NLR and changes in NLR on the incidence of reoperation in pediatric patients with COVID-19 and non-COVID-19.

Group	NLR	Re-surgery				*p*
		Yes		No		
		N	Median (min - max)	N	Median (min - max)	
COVID-19	Before Surgery	5	5,17 (1,01 - 9,61)	24	4,72 (0,18 - 34,61)	0,862
	After Surgery		3,74 (1,59 - 11,75)		5,14 (0,15 - 40,18)	0,817
	Change in NLR		0,57 (-5,20 - 6,58)		0,70 (-8,28 - 18,07)	0,513**
Non COVID-19	Before Surgery	10	6,22 (0,67 - 8,79)	48	3,87 (0,2 - 24,51)	0,463
	After Surgery		3,61 (2,31 - 5,74)		3,66 (0,26 - 32,59)	0,766
	Change in NLR		-0,86 (-5,18 - 1,64)		0,07 (-12,15 - 28,8)	0,606

Note: *mean ± standard deviation.
**Unpaired t-test.

Table 4. Differences in NLR and changes in NLR on the incidence of sepsis in pediatric patients with COVID-19 and non-COVID-19.

Group	NLR	Sepsis				*p*
		Yes		No		
		N	Median (min - max)	N	Median (min - max)	
COVID-19	Before Surgery	4	6,16 (3,67 - 34,61)	25	4,28 (0,18 - 12,87)	0,229
	After Surgery		10,85 (1,94 - 40,18)		3,74 (0,15 - 23,44)	0,129
	Change in NLR		5,92 (-5,20 - 6,58)		0,57 (-8,28 - 18,07)	0,533**
Non COVID-19	Before Surgery	16	3,45 (0,48 - 16,06)	42	3,95 (0,2 - 24,51)	0,226
	After Surgery		4,03 (1,34 - 6,65)		3,66 (0,26 - 32,59)	0,190
	Change in NLR		0,19 (-9,41 - 1,64)		0,01 (-12,15 - 28,8)	0,960

Note: *mean ± standard deviation.
**Unpaired t-test.

Table 5. Differences in NLR and changes in NLR on the incidence of septic shock in pediatric patients both with COVID-19 and non-COVID-19.

Group	NLR	Septic Shock				*p*
		Yes		No		
		N	Median (min - max)	N	Median (min - max)	
COVID-19	Before Surgery	4	6,13 (3,67 - 34,61)	25	4,28 (0,18 - 12,87)	0,255
	After Surgery		10,85 (4,28 - 40,18)		3,52 (0,15 - 23,44)	0,058
	Change in NLR		5,92 (-2,80 - 6,58)		0,57 (-8,28 - 18,07)	0,392**
Without COVID-19	Before Surgery	6	6 (0,48 - 16,06)	52	3,79 (0,2 - 24,51)	0,971
	After Surgery		6,2 (1,34 - 7,48)		3,61 (0,26 - 32,59)	0,720
	Change in NLR		0,19 (-9,41 - 1,7)		0,01 (-12,15 - 28,8)	0,527

Note: *mean ± standard deviation.
**Unpaired t-test.

Table 6. Differences in NLR and changes in NLR on the incidence of mortality in pediatric patients with COVID-19 and non-COVID-19.

Group	NLR	Mortality				*p*
		Yes		No		
		N	Median (min - max)	N	Median (min - max)	
COVID-19	Before Surgery	5	7,08 (3,67 - 34,61)	24	3,93 (0,18 -11,58)	0,073
	After Surgery		9,94 (4,28 - 40,18)		3,04 (0,15 -23,44)	0,050
	Change in NLR		5,57 (-4,61 - 6,58)		0,61 (-8,28 - 18,07)	0,817**
Non COVID-19	Before Surgery	14	5,78 (0,48 -16,06)	44	3,87 (0,2 - 24,51)	0,342
	After Surgery		5,74 (1,34 - 7,48)		3,56 (0,26 -32,59)	0,434
	Change in NLR		0,86 (-9,41 - 2,19)		-0,2 (-12,15 - 28,8)	0,978

Note: *mean ± standard deviation.
**Unpaired t-test.

Table 7. Comparison of changes in NLR in pediatric patients with COVID-19 and non-COVID-19 who experienced re-surgery, sepsis, septic shock, and mortality.

Variables		Change in NLR				*p-value*
		COVID-19		Non COVID-19		
		N	Median (min - max)	N	Median (min - max)	
Re-surgery	Yes	5	0,57 (-5,20 - 6,58)	10	-0,86 (-5,18 - 1,64)	0.806
	No	24	0,70 (-8,28 - 18,07)	48	0,07 (-12,15 - 28,8)	0.145

(Table 7) contd.....

Variables		Change in NLR				*p-value*
		COVID-19		Non COVID-19		
		N	Median (min - max)	N	Median (min - max)	
Sepsis	Yes	4	5,92 (-5,20 - 6,58)	16	0,19 (-9,41 - 1,64)	0.131
	No	25	0,57 (-8,28 - 18,07)	42	0,01 (-12,15 - 28,8)	0.361
Septic Shock	Yes	4	5,92 (-2,80 - 6,58)	6	0,19 (-9,41 - 1,7)	0.136
	No	25	0,57 (-8,28 - 18,07)	52	0,01 (-12,15 - 28,8)	0.384
Mortality	Yes	5	5,57 (-4,61 - 6,58)	14	0,86 (-9,41 - 2,19)	0.267
	No	24	0,61 (-8,28 - 18,07)	44	-0,2 (-12,15 - 28,8)	0.336

Table **6** presents a statistical analysis of differences in NLR and changes in NLR on the incidence of mortality in both groups. The results of the analysis showed that there was no significant difference between changes in NLR and mortality in both groups, with a significance value in the COVID-19 group of 0.817 and non-COVID-19 group of 0.978.

As mentioned in Table **7**, there was no significant difference between changes in NLR in both groups who experienced or did not experience re-surgery, sepsis, septic shock, and mortality.

4. DISCUSSION

Pediatric patients with COVID-19 who underwent surgery had more favorable post-surgical outcomes and better short-term outcomes than adult patients with COVID-19, with no reported cases of mortality and fewer complications. These results may help in decision-making for pediatric surgery during the COVID-19 pandemic. Several studies have shown frequent pulmonary complications and other complications, such as hypercoagulation and multi-inflammatory syndrome in children [15].

Our study found that NLR after surgery tends to decrease compared to before surgery, but if we consider the NLR meter by Zahorec, both groups are in the mild and moderate zones. This is different, where the surgical process will cause acute inflammation, which will increase neutrophils; even though there is additional inflammation with COVID-19 infection, there is no increase in neutrophils [16, 17]. Several studies have evaluated the relationship between NLR and outcomes and have shown worse outcomes with increasing NLR. Prasetya D (2019) found that pediatric patients undergoing appendicitis surgery obtained a high NLR and showed that the NLR has a high accuracy for diagnosing appendicitis in children, which is more sensitive than leukocytosis, but different from our study because there was a tendency to decrease NLR after surgery and even severe neutropenia in some cases [5].

This study found a decrease in NLR in the COVID-19 and non-COVID-19 groups. However, it was not significant in both groups, in contrast to adults. In adults, NLR is a predictive value for disease severity accompanied by COVID-19, as revealed by Jimeno S *et al*. in adult patients [13].

Folino *et al*. (2022) found that neutropenia among children hospitalized for COVID-19 infection was 12.63%, which was lower than the existing research data, *i.e*., 23%-26% [18, 19]. Our study indicated the same thing where the number of children with COVID-19 in 29 samples who had neutropenia was 25%, while the samples with death due to COVID-19 had a greater decrease in the number of neutrophils or severe neutropenia.

Incidental neutropenia is commonly observed mostly in association with some viral infections in childhood and occasionally reported in SARS-CoV-2 infection. Virus-associated neutropenia is related to the virus-induced redistribution of neutrophils from the circulation to the marginal pool; it usually occurs 24-48 hours after infection and persists for 3-8 days, which is generally associated with a period of viremia [18]. It mostly involves young children under 2 years of age. Venturini *et al*. (2020) reported two cases of severe transient neutropenia in two infants aged 23 and 39 days during mild COVID-19 [19-21].

Based on several previous studies, it was found that more cases of children with COVID-19 experienced neutropenia than lymphocytopenia, where it was associated with higher levels of natural killer (NK) in the blood and also related to an effective innate immune system and ACE-2 maturity, which was the reason for the appearance of milder symptoms [23]. Similarly, our study also found more neutropenia than lymphocytopenia in children with COVID-19; this is in line with research by Bourkhissi *et al*. in Morocco in 2020, which found that 7% of children with COVID-19 had neutropenia compared to 3% who had lymphocytopenia [22, 23].

5. CHANGES IN NLR AND LENGTH OF STAY IN PEDIATRIC PATIENTS WITH COVID-19 AND NON-COVID-19

The length of stay of COVID-19 patients undergoing surgery was in line with research by Giwangkancana *et al*.

in Indonesia (2022), which reported a length of stay of 12 ± 13.3. Our study obtained a change in NLR of 0.64 (-8.28 - 18.07) in COVID-19 patients, who were discharged from the hospital (86%). These results were in line with the results of a study by Jimeno *et al.* in Spain, in which, in the COVID-19 adult population, patients with a change in NLR = 1 were 68 (60%) who were discharged from the hospital. So, based on the results of our study, the possibility of discharge from hospitalization was higher if the change in NLR increased <1 or in patients with mild and moderate degrees of inflammation.

Our study was in line with research by C. Nielson BS *et al.* (2022) that there is no significant difference between pediatric patients with COVID-19 and non-COVID-19 on the average length of hospital stay. This indicates that the increased risk of pulmonary complications due to viral infections and the presence of inflammation due to surgery are not interrelated. The same finding was also found by Mehl *et al.* (2021) that pediatric surgery with COVID-19 has good surgical outcomes with an average length of stay of 4 days in various surgical procedures, a condition that is very different in adults undergoing surgery.

6. CHANGES IN NLR ON THE INCIDENCE OF REOPERATION, SEPSIS, SEPTIC SHOCK, AND MORTALITY IN PEDIATRIC PATIENTS WITH COVID-19 AND NON-COVID-19

In both groups who underwent reoperation, the movement of NLR towards low stress showed that hyperinflammatory factors were not too prominent in both groups. This could be due to the use of anti-inflammatories and antibiotics before and during the surgical process, while other risk factors increase dehiscence causing reoperation in children, namely nutritional factors, albumin levels, age less than one year, infected surgical wounds, median incisions, emergency surgery. In our study, one of the factors causing the operation is nutritional factors, where 28.7% of the samples were malnourished; 9.2% in the COVID-19 group and 19.5% in the non-COVID-19 group.

In the COVID-19 group, sepsis and septic shock had a higher NLR than the group without COVID-19, and both groups were in the mild to moderate inflammatory area. However, at post-surgery, there was a difference in NLR in the two groups, but post-surgery, in the COVID-19 group, there was a change in NLR to moderate and severe inflammation. Our study was in line with the study by Bari *et al.* (2021), demonstrating that the average NLR of children suffering from COVID-19 symptoms is mild-moderate compared to severe-critical, where there are 8% of children who undergo surgery with COVID-19. The results of our study were also in line with the results of a study by Khadijah S et al., which found that the median NLR of neonates with sepsis without COVID-19 was 3.63 (2.39 - 6.12) with a cut-off NLR of 2.12 having a risk of sepsis of 1.8 times.

Based on the results of our study, it can be seen that COVID-19 infection increases NLR and changes in NLR, but the results of surgical outcomes with the incidence of sepsis and septic shock are not statistically significant.

Regarding the NLR before surgery related to the incidence of mortality based on the Zahorec NLR meter, the COVID-19 group had moderate and severe inflammation, while non COVID-19 group had mild and moderate inflammation. Moreover, there was an increase in NLR only in the COVID-19 group compared to non-COVID-19, although there was no significant difference. Y. Tekin reported that the NLR at the time of admission in pediatric trauma patients without COVID-19 with a cut-off of 2.77 increases the risk of death by 3.21. This result is also the same as the results of the study by Jimeno et al., which reported that the mean of change in NLR at the time of admission of non-survival and survival patients was 2.5 times [14].

In our study, mortality cases were five out of 29 subjects in the COVID-19 group, where four patients had congenital abnormalities that required surgical correction, namely gastroschisis, jejunal atresia, hydrocephalus, and pineal tumor, and septic shock that preceded the mortality was reported in 4 patients. Hence, the mortality was due to the severity of inflammation and organ dysfunction accompanied by bacterial infection, whereas viral infection could have caused it but did not directly cause mortality.

A limitation of our study is that the pediatric patients with COVID-19 and non-COVID-19 in this study had a variety of conditions because this was an emergency operation.

CONCLUSION

There is no difference in the outcome of surgery for children with COVID-19 and without COVID-19 based on the NLR change analysis.

LIST OF ABBREVIATIONS

ACE-2	=	Angiotensin Converting Enzyme-2
ASA PS	=	American Society of Anesthesiologists Physical Status
CHA	=	Children's Hospital Association
COVID-19	=	Corona Virus Disease-19
CRP	=	C-Reactive Protein
ICU	=	Intensive Care Unit
IDAI	=	Indonesian Pediatric Association
NK	=	Natural Killer
NLR	=	Neutrophil-Lymphocyte Ratio
RT-PCR	=	Real-Time Polymerase Chain Reaction
SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus-2

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical Approval was given by Hasanuddin University

Faculty of Medicine Ethics Committee with reference number: 477/UN4.6.4.5.31/PP36/2022 2. Ethical Approval was given by RSUD Dr. Soetomo Health Research Ethics Commitee with reference number: 1112/LOE/301.4.2/X/2022 3. Ethical Approval was given by RSUD Ulin Banjar masin Hospital Research and Ethical Committee with ref ference number:239/XI-Reg Riset/RSUDU/22.

HUMAN AND ANIMAL RIGHTS

No animals were used in the studies that are the basis of this research. The experimentation on humans was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants of this study.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

STANDARDS OF REPORTING

STROBE guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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