

The correlation between neutrophil lymphocyte ratio in pregnant women with COVID-19 and neonatal outcome

By Wilda Haliza

TYPE OF ARTICLE: Clinical Studies

The correlation between ⁷neutrophil lymphocyte ratio in pregnant women with COVID-19 and neonatal outcome

Wilda Haliza¹, Martono Tri Utomo¹, Kartika Darma Handayani^{1*}

¹²Department of Child Health, Faculty of Medicine, Airlangga University, Dr. Soetomo General Academic Hospital, Surabaya, East Java, Indonesia

CORRESPONDING AUTHOR: Prof. ²¹Martono Tri Utomo

Email: martono.utomo73@gmail.com



ABSTRACT

Background and Objectives. Coronavirus Disease 2019 (COVID-19) in pregnancy periods can adversely affect the neonatal outcomes. Neutrophil Lymphocyte Ratio (NLR) were reported as sensitive markers and good predictor of COVID-19 progression in symptomatic pregnant women. The aim of this study to find correlation on NLR value of the pregnant women with COVID-19 to the neonatal outcome.

Materials and Methods. We retrospectively included neonates who was delivered from pregnant women with COVID-19 at Dr. Soetomo Hospital from June 2021 to July 2022. NLR value of the pregnant women were calculated. Demographic data and clinical characteristic were taken from medical records. The diagnosis of COVID-19 in pregnant women is confirmed by PCR nasopharyngeal swab, as well as in the neonates who undergo nasopharyngeal swab a maximum of 24 hours after birth.

Results. Total of 1058 births delivered between June 2021- July 2022, 224 neonates (21.17%) met inclusion criteria. We analyzed the severity of maternal factors described by NLR and correlated with neonate outcomes, such as mortality, Apgar Score (AS), birth weight, gestational age, type of delivery and Polymerase Chain Reaction (PCR) swab of the neonates. the results of our analysis, the maternal NLR was correlated with the birth weight ($p=0.005$). However, NLR of the pregnant women are not correlated with mortality of the neonates ($p=0.681$), type of delivery ($p= 1$), AS at 1 minute ($p= 0.158$), AS at 5 minutes ($p=0.158$), gestational age ($p=0.110$) length of stay (LOS) ($p=0,258$) and PCR swab of the neonates ($p= 1$).

Conclusions. NLR value in the majority of pregnant women with COVID-19 was found to be increasing, but these results are not related for the neonatal outcome except the birth weight.

Keywords: neutrophil lymphocyte ratio, covid-19, pregnant women, neonates



Abbreviations:

AS : *Apgar Score*

²⁵
CBC : *Complete Blood Count*

COVID-19 : *Corona Virus Disease- 19*

LOS : *Length of Stay*

NLR : *Neutrophyl Lymphocyte Ratio*

¹³
NICU : *Neonatal Intensive Care Unit*

PPE : *Personal Protective Equipment*

POGI : *Persatuan Obstetric Ginekologi Indonesia*

²⁰
PCR : *Polymerase Chain Reaction*

SPSS : *Statistical Package for the Social Sciences*



11

INTRODUCTION

The COVID-19 pandemic, which has been announced by World Health Organization (WHO) since January 2020, has had a negative impact on majority sectors of life, specifically health sector. Government policy by implementing social restrictions affects the health sector, especially the health of pregnant women which is influenced by the system and access to health services, the availability of qualified health services and access to health information and education during the nine months of pregnancy [1].

NLR is an inflammatory biomarker from a simple complete blood count (CBC) test by comparing the absolute number of neutrophils and lymphocytes which can predict the level of severity and predict endothelial damage related to the inflammatory processes [2]. This examination is cheap, simple and has long been used as a predictor of morbidity and mortality in patients with cancer, heart disease, sepsis in various conditions and this examination is available at almost all existing health facilities [3].

COVID-19 in pregnant women can have a negative impact in outcomes of the neonates. Several studies have been published about the use of NLR as a short-term prognostic marker in patients with COVID-19. Meanwhile, in pregnant women with COVID-19, NLR is a very meaningful clinical marker for determining maternal health and the risk of various pregnancy complications, including prematurity, miscarriage and low birth weight [4,5]. NLR was reported as a sensitive marker for the development of COVID-19 in symptomatic pregnant women, with NLR sensitivity and specificity of 91.8% and 66.4%, respectively [6]. Nevertheless, until now, the correlation condition of the neonates who delivered from pregnant women with COVID-19 and allegations of vertical transmission is still unclear and unexplored. Therefore, the aim of this study is to investigate the correlation NLR of the pregnant women with COVID-19 with the neonatal outcome.



32

MATERIALS AND METHODS

A descriptive observational study was performed, which included newborn who delivered from pregnant women with COVID-19. The study took place between June, 2021 until July, 2022 at Dr. Soetomo Hospital, Surabaya. The maternal characteristic data with laboratory results and characteristic of the neonates was taken. We took the pregnant women's laboratory data from the closest data before delivery and classify the NLR into normal and elevated with the cut off poin is 3.13. The characteristics of the neonates include: mortality, birth weight, AS at 1 and 5 minutes, PCR swab, type of delivery and LOS. The examination of PCR swab COVID-19 of the neonates was taken on 24 hours after delivery and the neonates was treated on Neonatal Intensive Care Unit (NICU).

The inclusion criteria were: neonates who delivered from pregnant women with COVID-19 at Dr. Soetomo Hospital. The diagnose of COVID-19 confirmed by RT PCR testing of nasopharyngeal swab.

The study was granted the ethical clearance by the Ethical Committee of Dr. Soetomo General Academic Teaching Hospital (Research ID: 1528/105/3/VII/2022).

Data Analysis

The data collecting sheet contains all of the data. The study data were entered into IBM SPSS Statistics Version 21 after being coded and tabulated. To assess the research hypothesis, data analysis techniques included inferential testing and descriptive analysis. A table with descriptive data is displayed.

A normalcy test is used to conduct the inferential test. In cases where the variables were regularly distributed, the analysis would employ the Spearman test; in other cases, Pearson correlation would be utilized. If the p-value was ≤ 0.05 , the analysis's findings and the mean difference between the variables were declared to be significant.



RESULTS

During the analyzed period (June 1st, 2021 until July 31st, 2022), there are 1058 births, of which 224 neonates (21.17%) were delivered from pregnant women with COVID-19 confirmed. Characteristic of subject is described in table 1.

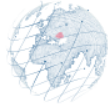
Table 1. Characteristics of subjects

Pregnant Women (n=217)	Mean±SD n (n%)
Age (years)	29.73±6.23
LOS (days)	3.2±6.2
Outcome	
Alive	197 (87.9%)
Death	27 (12.1%)
NLR	8.96±7.65
Normal	20 (8.9%)
Elevated	204 (91.1%)
Neonates (n = 224)	
Birth weight (grams)	2603.08±727.2
Type of delivery	
Spontaneous	55 (24.6%)
Caesarean	169 (75.4%)
Gestational age (weeks)	36.3±3.5
AS at 1 minute	6.2±1.56
AS at 5 minutes	7.6±1.3
PCR swab	
Negative	216 (96.4%)
Positive	8 (3.6%)
Outcome	
Alive	205 (91.5%)
Death	19 (8.5%)
LOS (days)	7.32±7.8

The mean of age is 29.73±6.23 years, with most of pregnant women were alive (87.9%). The overall mean of NLR was 8.96±7.65 and 91.1% pregnant women have elevated NLR. More over, the average birth weight of the neonates was 2603.08±727.2 grams and most of them delivered by C-Section (75.4%) with the mean of gestational age is 36.3±3.5 weeks. 5 minutes AS is 7.6±1.3 and more than 90% of the neonates had PCR swab negative and remain alive.

Correlation NLR pregnant women with COVID-19 with the neonatal outcome describe on table 2.

Table 2. Correlation NLR of pregnant women with COVID-19 with the neonatal outcome



Variables	p-value
Birth weight	0.005
Gestational age	0.110
Type of delivery	1
AS at 1 minute	0.158
AS at 5 minutes	0.707
LOS	0.258
PCR Swab	1

Only birth weight was significantly correlated ($p=0,005$). Further more, other variables are not.

DISCUSSION

There are 224 neonates included to this study and more than half of them (75.4%) was delivered by caesarean section. In previous meta-analysis concluded that pregnant women with COVID-19 had an increased of absolute risk for caesarean delivery compared with pregnant women without COVID-19 [7]. The increased of caesarean delivery can be explained by the fact, especially at the beginning of the pandemic, caesarean delivery was believed to have lower risk of transmission of infection to health workers and to save on the use of Personal Protective Equipment (PPE) as well as Persatuan Obstetri Ginekologi Indonesia (POGI) recommendation which stated that confirmed cases of COVID-19 should be terminated by caesarean [8,9]. In our knowledge there was no study correlate NLR of the pregnant women with COVID-19 with type of delivery and our study did not find correlation.

The health of women during pregnancy and the fetus is influenced by health system and access to health services, availability of health services and access to health information and education [1]. Effect of lockdown restrictions due to COVID-19 pandemic has resulted in a decrease of prenatal visits.

The changes of anatomy, physiology and biochemistry during pregnancy, consequently in this group, being at high risk of infected by COVID-19 and worsening condition such as admission in intensive care, using invasive ventilation, giving birth prematurely and death. Study in Nepal,



Zimbabwe and South Africa in 2020, there was a decrease in prenatal visits and a significant increase in neonatal mortality rate [10–12].

This study found a significant correlation between NLR with birth weight of the neonates. Previous prospective study revealed similar result NLR correlate with birth weight of the neonates on pregnant women without COVID-19 [13]. Specifically, ⁷ study by Panwar et al., 2020 concluded that an increase in maternal NLR in the second trimester of pregnancy (16-18 weeks) influences the incidence of low birth weight [14]. This is in accordance with theory that an increase on NLR is an indicator of histological chorioamnionitis on prenatal period. And this theory is the same as hypothesis that stated of increased of NLR caused by maternal hyperinflammation can cause fetal growth restriction and prematurity [15].

Many studies stated that COVID-19 is transmitted vertically and placenta is a potential target. Process of thrombosis and inflammation results in ⁹ inadequate uteroplacental perfusion and oxygenation which results in placental ischemia and abnormal angiogenesis ⁹ which is to be main cause of fetal intrauterine growth restriction and decreased growth rate in the fetus. This mechanism will occur if infection at second and third trimesters [16]. Unfortunately, this study can not determine when infection occurred and causes other than infection was not excluded.

Apgar scoring is recorded in all newborn at 1 and 5 minutes, low score associated with asphyxia. In pregnant woman with COVID-19, placental ischemia and thrombosis are suspect related to asphyxia in neonates. The process was decreased oxygenation, changes in the heart rate, effort of breathing and lack of response to stimuli ²⁶ [17]. In this study did not find a significant correlation ⁶ between NLR of the pregnant women infected with COVID-19 and AS of the neonates at the 1 and 5 minutes.

We have not found the same study, but there are several similar studies on ⁸ pregnant women without COVID-19. A cohort study in India stated that high NLR in pregnant women were associated with low birth weight and poor of AS [5]. Despite did not relate to infection biomarkers, ¹³ a



retrospective cohort study conducted for eight months in Malaysia found that significant maternal vascular thrombosis in a group of pregnant women with COVID-19. The changes of placental villous maturation in group of severe critical condition were associated with an increased risk of low AS and maternal mortality [18].

In our study we also did not find significant correlation between NLR of the pregnant women with COVID-19 with the incidence of prematurity. We have not found the same study yet. However, a retrospective study in Turkey stated that NLR can predict the preterm birth by high sensitivity and specificity [4].

1 *Limitation of the study*

Our study has several limitations: 1). This study was only conducted in one health center with a narrow period and limited subject; 2). Nowadays researchs about COVID-19 was progressively evolved. many studies revealed there are other factors affected to COVID-19 outcome such as infection biomarker, strain of COVID-19 and pregnant women vaccination status. However, that are not studied in this paper; 3). Other factors that affected to NLR was not involve in this study.

CONCLUSIONS

This study showed that NLR of the pregnant women with COVID-19 was only associated with the birth weight of the neonates.

17 **CONFLICT OF INTEREST**

The authors have no conflict of interest to disclose.

AUTHOR'S CONTRIBUTIONS



Conceptualization, W.H, M.T.U and K.D.H; methodology, W.H and M.T.U; software, W.H; validation W.H, M.T.U and K.D.H.; formal analysis, W.H.; investigation, W.H.; resources, M.T.U and K.D.H; **3** data curation, W.H.; writing—original draft preparation, W.H.; writing—review and editing, M.T.U and K.D.H.; visualization, W.H.; supervision, M.T.U and K.D.H.; project administration, W.H.; funding acquisition, W.H. All authors have read and agreed to the published version of the manuscript.

1

ACKNOWLEDGEMENTS

We would like to thank our Head of Department of Child Health, Muhammad Faizi, MD, PhD. We also would like to appreciate the help of all staff in Department of Child Health for supporting and giving warm motivation for authors to complete this study.



REFERENCES

1. Fatmaningrum, D. A., Anis, W., Laksana, M. A. C. The Impact of the COVID-19 Pandemic on Maternal Mortality Attributes. *Indonesian Journal of Health Administration*. 2022; 10(1): 70–8. doi:<https://doi.org/10.20473/jaki.v10i1.2022.70-78>.
2. Lira, SC., Espinosa, MG. Differences in the Neutrophil/Lymphocyte Ratio and the Platelet/Lymphocyte Ratio in Pregnant Women with and without COVID-19. *International Journal of Gynaecology Obstetric*. 2021; 00:1-7. doi: 10.1002/ijgo.13840
3. Alkhatip, AAAM., Kamel, MG., Hamza, MK., Farag, EM., Yassin, HM., Elayashy, M et al. The diagnostic and prognostic role of neutrophil- to-lymphocyte ratio in COVID-19: a systematic review and meta-analysis. *Expert Review of Molecular Diagnostics*. 2021; 21: 505-14. doi: 10.1080/14737159.2021.1915773.
4. Yuce, E. Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) Can Predict Spontaneous Preterm Birth? *Journal of Inflammation Research*. 2023; 16: 2423-9. doi:<https://doi.org/10.2147/JIR.S414305>.
5. Panwar, M., Mohanty, A., Ahuja, N., Anand, HP., Kamble, BK. Maternal β -HCG and Neutrophil Lymphocyte Ratio during Pregnancy to Predict High-Risk Neonates: An Observational Study. *Maedica: Journal of Clinical Medicine*. 2022; 17(2): 317-22. doi:<https://doi.org/10.26574/maedica.2022.17.2.317>.
6. Selanno, Y., Widaningsih, Y., Esa, T., Arif, M. Analysis of Neutrophil Lymphocyte Ratio and Absolute Lymphocyte Count as Predictors of Severity of COVID-19 Patients. *Indonesia Journal of Clinical Pathology and Medical Laboratory*. 2021; 27(2): 184-9.
7. Allotey, J., Fernandez, S., Bonet, M., Stallings, E., Yap, M., Kew, T et al. Clinical Manifestations, Risk Factors, and Maternal and Perinatal Outcomes of Coronavirus Disease 2019 in Pregnancy: Living Systematic Review and Meta-Analysis. *The British Medical Journal*. 2020; 370. doi: <http://dx.doi.org/10.1136/bmj.m3320>.
8. Akbar, MIA., Gumilar, KE., Andriya, R., Wardhana, MP., Mulawardhana, P., Anas, JY. Clinical Manifestations and Pregnancy Outcomes of COVID-19 in Indonesian Referral Hospital in Central Pandemic Area. *Obstetrics & Gynecology Science*. 2022; 65(1): 29-36. <https://doi.org/10.5468/ogs.21135>.
9. Anggraini, NWP., Sulistyowati, S. Low neutrophil-to-lymphocyte ratio decreases risk of coronavirus disease in pregnant women. *Universa Medicina*. 2020; 39: 88-96. doi: 10.18051/UnivMed.2020.v39.88-96



10. Kc, A., Gurung, R., Kinney, MV., Sunny, AK., Moinuddin, M., Basnet, O., et al. Effect of the COVID-19 Pandemic Response on Intrapartum Care, Stillbirth, and Neonatal Mortality Outcomes in Nepal: A Prospective Observational Study. *The Lancet Global Health*. 2020; 8 (10): 1273-81. doi:[https://doi.org/10.1016/S2214-109X\(20\)30345-4](https://doi.org/10.1016/S2214-109X(20)30345-4).
11. Murewanha, G., Nyakanda, MI., Madziyire, MG. Restoring and Maintaining Robust Maternity Services in the COVID-19 Era: a Public Health Dilemma in Zimbabwe. *Pan African Medical Journal*. 2020; 37: 1-9. doi:<https://doi.org/10.11604/pamj.suppl.2020.37.1.26798>.
12. Milimouno, TM., Dioubaté, N., Niane, H., Diallo, MC., Maomou, C., Sy, T., et al., Effect of the COVID-19 Pandemic on Maternal and Neonatal Health Service in Three Referral Hospital in Guinea: an Interrupted Time-Series Analysis. *Reproduction Health*. 2023; 1-13. doi:<https://doi.org/10.1186/s12978-023-01599-8>.
13. Akgun, N., Kalem, MN., Yuce, E., Kalem, Z., Hatice, A. Correlations of maternal neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) with birth weight. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2017; 30:2086–91. <http://dx.doi.org/10.1080/14767058.2016.1237497>
14. Panwar, M., Mohanty, A., Ahuja, N., Anand, HP., Kamble, BK. Maternal β -HCG and Neutrophil Lymphocyte Ratio during Pregnancy to Predict High-Risk Neonates: An Observational Study. *Maedica: Journal of Clinical Medicine*. 2019; 13: 34-7. <https://doi.org/10.26574/maedica.2022.17.2.317>
15. Balciuniene, G., Kvederaite-Budre, G., Gulbiniene, V., Dumalakiene, I., Viliene, R., Pilypiene, I et al. Neutrophil–lymphocyte ratio for the prediction of histological chorioamnionitis in cases of preterm premature rupture of membranes: a case-control study. *BMC Pregnancy and Childbirth*. 2021; 21: 656. doi: <https://doi.org/10.1186/s12884-021-04101-z>.
16. Tela, FG., Bezabih, AM., Adhanu, AK. Effect of pregnancy weight gain on infant birth weight among mothers attending antenatal care from private clinics in Mekelle City, Northern Ethiopia: A facility-based follow-up study. *PloS One*. 2019; 14: 1-10. doi: <https://doi.org/10.1371/journal.pone.0212424>.
17. Dalili, H., Nili, F., Sheikh, M., Hardani, AK., Shariat, M., Nayeri, F. Comparison of the Four Proposed Apgar Scoring Systems in the Assessment of Birth Asphyxia and Adverse Early Neurologic Outcomes. *PLoS One*. 2015; 10:1-9. DOI:10.1371/journal.pone.0122116
18. Wong, YP., Tan, GC., Omar, SZ., Mustangin, M., Singh, Y., Salker, MS., et al. SARS-CoV-2 Infection in Pregnancy: Placental Histomorphological Patterns, Disease Severity and Perinatal

Outcomes. International Journal of Environmental Research and Public Health. 2022; 19(15):
9517. doi: <https://doi.org/10.3390/ijerph19159517>.