Indonesian Journal of Medicine (2022), 07(04): 401-410
Masters Program in Public Health, Universitas Sebelas Maret

Research

Analysis of the COVID-19 Severity Based on NLR and the Mortality Rate of Pregnant Women with COVID-19 at Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia

Dhea Fitria Rachma[1)], Teguh Prakosa[2)], Sigit Setyawan[3)], Abdurahman Laqif[2)]

[1)]Medical student, Faculty of Medicine, Universitas Sebelas Maret
[2)]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sebelas Maret
[3)]Department of Parasitology, Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is a disease of the human respiratory system. Pregnant women are more susceptible to respiratory infections due to physiological changes in the immune and cardiopulmonary systems. Routine laboratory biomarkers such as lymphocytes, neutrophils, and NLR are considered prognostic in COVID-19. This study aimed to analyzed the severity of COVID-19 based on NLR on the mortality of pregnant women with COVID-19 at Dr. Moewardi, Surakarta.
Subjects and Method: This study used analytic observational with a cross-sectional. The study subjects were 82 pregnant women with confirmed COVID-19, aged over 18 years, and being treated at RSUD Dr. Moewardi Surakarta between March 2020 to January 2022. The samples were taken using the consecutive sampling technique. The independent variable is the severity of COVID-19 based on clinical presentation. The dependent variable is the laboratory results in lymphocytes, neutrophils, and NLR. Data were collected from medical records and anlayzed using SPSS software.
Results: There was correlation between NLR on the severity of pregnant women with COVID-19 (Mean= 10.11; SD= 4.10; p= 0.026) and there was a significant correlation between NLR on the mortality rate of pregnant women with COVID-19 (Mean= 9.92; SD= 3.94; p<0.001).
Conclusion: NLR affected the severity and the mortality rate among pregnant women with COVID-19.

Keywords: COVID-19, pregnancy, lymphocytes, neutrophils, NLR, mortality

Correspondence:
Dhea Fitria Rachma. Faculty of Medicine Universitas Sebelas Maret Surakarta. Jl. Ir. Sutami 36A, Surakarta 57126, Indonesia. Email: dheaf1020@student.uns.ac.id. Mobile: 085702594898.

Cite this as:
Rachma DF, Prakosa T, Setyawan S, Laqif A (2022). Analysis of the COVID-19 Severity Based on NLR and the Mortality Rate of Pregnant Women with COVID-19 at Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia. Indones J Med. 07(04): 401-410. https://doi.org/10.26911/theijmed.2022.07.04.05.

BACKGROUND

Coronavirus Disease (COVID-19) is a disease that attacks the human respiratory system (Rothan and Byrareddy, 2020). COVID-19 is caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) and is highly contagious (Cascella et al., 2022).

The SARS-CoV2 virus infects and damages tissues in the human respiratory tract so that it can cause several clinical symptoms, such as fever, shallow breathing, cough, headache, muscle aches, diarrhea, fatigue, sore throat, anosmia, ageusia, chest pain, hemoptysis, sputum production, rhinorrhea, nausea, vomiting, skin

rashes, impaired consciousness to the occurrence of seizures (Krishnan et al., 2021). Based on the clinical symptoms caused, there is a classification of the severity of COVID-19 symptoms, namely asymptomatic or no symptoms, mild symptoms, moderate symptoms, severe symptoms, and critical (Kemenkes, 2021).

People who are vulnerable to COVID-19, including the elderly (> 65 years of age), people with weakened "immunecompromised" immune systems, such as those with other underlying infections or chronic illnesses, and pregnant women (Phoswa and Khaliq, 2020).

A report shows pregnant women have a high risk of respiratory virus infection and severe pneumonia due to physiological changes in the immune system and cardiopulmonary systems (Karimi et al., 2021). Other studies also state that pregnant women infected with COVID-19 have a higher risk of death than pregnant women without COVID-19. It was reported that there were 11 (1.6%) deaths out of 706 pregnant women infected with COVID-19 and only 1 (0.1 %) death from 1424 pregnant women without COVID-19 with a relative risk of 22.26%. The risk of death for pregnant women is 1.6%, which is 22 times higher than that of pregnant women without COVID-19 (Villar et al., 2021).

In COVID-19, there is a systemic infection that impacts hematopoietic and homeostasis. Biomarkers available in routine laboratory results, such as lymphocytes and neutrophils, are considered accurate to guide treatment and care. Meanwhile, the Neutrophil-Lymphocyte Ratio (NLR) helps in the prediction and prognosis of COVID-19 (Kerboua, 2021). Lymphocytes express ACE-2 receptors on their surface so that SARS-CoV-2 can infect these cells directly and an increase in cytokines causes lymphocyte apoptosis (Gavriatopoulou et al., 2020). This study aimed to analyze the correlation between the severity of COVID-19 based on NLR and the mortality of pregnant women with COVID-19 at RSUD Dr. Moewardi, Surakarta.

SUBJECTS AND METHOD

1. Study Design

This study used an analytic observational design by testing the hypothesis without providing intervention to the sample at RSUD Dr. Moewardi, Surakarta in May-July 2022. Data were collected from medical record data. The approach used in this research is cross-sectional.

2. Population and Sample

The target population in this study were pregnant women with confirmed COVID-19, aged over 18 years, and being treated at RSUD Dr. Moewardi Surakarta between March 2020 to January 2022. The total population was 602 patients. The sample size in this study was 82 samples taken by consecutive sampling techniques. Patients with incomplete history taking, incomplete physical examination results, incomplete blood test results, and no positive RT-PCR results were excluded from the study. Secondary data about the patient's clinical history were obtained through medical records, including the patient's diagnosis, severity at admission, examination results, and treatment results. All data was taken the first time the patient was treated.

3. Study Variables

The independent variable is the severity of COVID-19 based on clinical presentation, and the dependent variable is the laboratory results in the form of lymphocytes, neutrophils, and NLR.

4. Operational definition of variables

Patients with confirmed COVID-19 are proven by positive RT-PCR results. In this study, the severity of COVID-19 cases was

based on the WHO definition there are non-severe and severe cases.

Non-severe cases (asymptomatic/mild and moderate) are women with no symptoms, mild symptoms (COVID-19 with no signs of viral pneumonia or hypoxemia), and moderate symptoms (clinical signs of pneumonia without hypoxemia in room air). Severe cases (severe and critical) cases are women with dyspnea (respiratory rate > 30 breaths/min) and hypoxemia on room air, requiring oxygen therapy or mechanical ventilation (invasive or non-invasive).

5. Study Instruments

Patient medical records from March 2020 to January 2022.

6. Data analysis

Data analysis was performed using the contingency coefficient correlation test for categorical data. For numerical data, a normality test was performed using the Shapiro-Wilk test. Then the independent-samples t-test was used if the data were normally distributed, and the Mann-Whitney test was used if the data were not normally distributed. Statistical test results are meaningful if the p-value <0.05. The data obtained were analyzed using SPSS software.

7. Research Ethics

Research ethical issues including informed consent, anonymity, and confidentiality, were addressed carefully during the study process. The research ethical clearance approval letter was obtained from the Research Ethics Committee at Dr. Moewardi Hospital, Surakarta, Indonesia, No. 459/IV/-HREC/2022, on April 8, 2022.

RESULTS

1. Sample Characteristics

The sample for this study was 82 pregnant patients with COVID-19 at RSUD Dr. Moewardi, Surakarta. The characteristics of the research sample are based on age, the majority of the sample was <35 years old, namely 58 patients (70.7%), and the remaining 24 patients (29.3%) were >35 years old. Based on gestational age, the study sample was dominated in the third trimester, namely 71 patients (82%), and the least in the first trimester, namely three patients (3.7%). Based on the number of parities, most patients were multiparas, namely 57 patients (69.5%), and the rest were nulliparas, namely 25 patients (30.5%). Based on BMI, most patients had normal BMI, namely 38 patients (46.3%). Based on the severity of COVID-19, the majority of patients were not severe, 55 patients (67.1%) and the rest were severe, 27 patients (32.9%). Based on clinical manifestations, the majority of patients experienced clinical symptoms (symptomatic), namely 48 patients (58.5%) and the rest did not experience clinical symptoms (asymptomatic), namely 34 (41.5%). Of the 48 patients who experienced clinical symptoms, the most common clinical symptom experienced by patients was a cough, namely 42 patients (51.2%), second was shortness of breath, namely 34 patients (41.5%), and lastly was fever, namely 24 patients (29.3%). In this study, 30 patients (36.6%) died (see Table 1).

The average age of the study subjects was 30.5 years, with the youngest patient being 19 years old and the oldest being 44 years old. The average gestational age is 34.7 weeks. Based on the characteristics of the body mass index, the average patient has a BMI of 24.6 kg/m2. From the measurement of the patient's clinical signs, the patient's average respiratory rate was 22.6 x/minute, and the average temperature was 36.6 oC. Based on laboratory results, the patient's lowest hemoglobin was 6.1 g/dl, and the highest was 14.5, with an average is 11.3. The lowest leukocyte count was 5 x 103/mm3, and the highest was 26.3 x

103/mm3, with an average of 11.8 x 103/mm3. The patient's average platelet count was 266.7 x 103/mm3, with the lowest score being 48 x 103/mm3 and the highest score being 575 x 103/mm3. The patient's mean neutrophil was 82.4%, and the patient's lymphocyte average was 12.7%. The value of the Neutrophil Lymphocyte Ratio (NLR) was obtained as low as 1.6 and as high as 33.3, with an average of 8.4 and a standard deviation of 4.9 (see Table 2).

Table 1. Characteristics of the sample (categorical data)

Characteristics	Category	Frequency	Percentage
Age	<35 years	58	70.7 %
	≥35 years	24	29.3 %
Gestational age	Trimester I	3	3.7 %
	Trimester II	8	9.8 %
	Trimester III	71	82 %
Parity	Nullipara	25	30.5%
	Multipara	57	69.5%
BMI	Underweight (<18.5 km/m^2)	5	6.1%
	Normal (18.5-25 km/m^2)	38	46.3 %
	Overweight (>25 km/m^2)	29	35.4 %
Severity	Severe	27	32.9%
	Non-severe	55	67.1%
Mortality	Death	30	36.6%
	Alive	52	63.4%
Clinical Manifestation	Asymptomatic	34	41.5 %
	Symptomatic	48	58.5%
	Cough	42	51.2 %
	Shortness of Breath	34	41.5 %
	Fever	24	29.3 %

Table 2. Sample characteristics (continuous data)

Variable	Mean	SD	Min.	Max
Ages (years)	30.5	6.3	19	44
Gestational age (weeks)	34.7	7.3	8	41
BMI (kg/m^2)	24.6	4.5	16.2	39.2
Respiration (x/minute)	22.6	5.3	16	44
Temperature (^{o}C)	36.6	0.54	36	38.6
Hemoglobin (g/dl)	11.3	1.5	6.1	14.5
Total Leukocytes (x10^3/mm^3)	11.8	4.9	5	26.3
Platelets (x10^3/ mm^3)	266.7	95.8	48	575
Neutrophil (%)	82.4	7.1	55	93.3
Lymphocytes (%)	12.7	5.9	2.8	34.6
NLR (%)	8.4	4.9	1.6	33.3

2. Bivariate Analysis

The bivariate analysis of categorical data used in this study was the contingency coefficient correlation test. Based on table 3, it is showed r = 0.36 which indicates a weak correlation between gestational age and severity but statistically shows a significant correlation with p= 0.002 (Table 3).

Table 3. Data analysis (analysis using contingency coefficient correlation test)

Variable	Non Severe (n = 55)	Severe (n = 27)	r_k (Contingency Coefficient)	p
Age			0.119	0.279
<35 years	41 (70.7%)	17 (29.3%)		
≥35 years	14 (58.3%)	10 (41.7%)		
Gestational Age			0.357	0.020
Trimester I	2 (66.7%)	1 (33.3%)		
Trimester II	1 (12.5%)	7 (87.5%)		
Trimester III	52 (73.2%)	19 (26.8%)		
Parity			0.232	0.310
Nullipara	21 (84%)	4 (16%)		
Multipara	34 (59.6%)	23 (40.4%)		
BMI			0.187	0.225
Underweight (<18.5 kg/m²)	4 (80%)	1 (20%)		
Normal (18.5-25 kg/m²)	35 (72.9%)	13 (27.1%)		
Overweight (>25 kg/m²)	16 (55.2%)	13 (44.8%)		
Mortality			0.656	0.001
Death	4 (13.3%)	26 (86.7%)		
Alive	51 (98.1%)	1 (1.9%)		
Clinical Manifestation			0.508	0.001
Asymptomatic	34 (100%)	0 (0%)		
Symptomatic	21 (43.8%)	27 (56.3%)		

Table 4. Data analysis (analyzed using independent-samples t-test and Mann-Whitney)

Variable	Category	Non Severe (n= 55)		Severe (n= 27)		p
		Mean	SD	Mean	SD	
Age		29.4	6.6	32.7	5.1	0.016
Gestational age		36.6	6.5	30.9	7.3	0.001
BMI		24.2	4.6	26.6	4.6	0.090
Clinical	Respiratory (x/min)	19.9	2.0	27.9	5.9	0.001
	Temperature (°C)	36.6	0.4	36.8	0.7	0.099
Hematological Parameters	Hemoglobin (g/dl)	11.4	1.3	10.9	1.8	0.111
	Total Leukocytes (x10³/mm³)	11.1	4.4	13.2	5.8	0.152
	Platelets (x10³/ mm³)	248.2	74.8	304.4	121.5	0.043
	Neutrophils (%)	80.6	7.6	86.1	4.2	0.001
	Lymphocytes (%)	14.1	6.5	9.8	3.5	0.001

Based on table 4, statistically, there is no significant difference between hemoglobin, leukocyte, platelet, neutrophil, and lymphocyte counts in severe and non-

severe COVID-19. However, the mean of platelets (×103) was 248.2 in the non-severe group and 304.4 in the severe group. This shows that patients with severe COVID-19 had a mean higher platelet count than those with non-severe COVID-19 (p-value 0.043). The mean neutrophils (%) in the non-severe group was 80.6 and in the severe group was 86.1, indicating that severe COVID-19 patients had a higher average neutrophil than non-severe COVID-19 (p-value 0.001). The average lymphocyte (%) in the non-severe group was 14.1 and in the severe group was 9.8, indicating that severe COVID-19 patients had a lower average lymphocyte compared to non-severe COVID-19 (see Table 4).

Table 5, shows the test results with a value of p = 0.026 (p<0.05). Because the p-value <0.05, the test results were declared significant, meaning there was a difference in the average NLR between the severe and non-severe groups. The mean of NLR in the severe group = 10.11 with a standard deviation = 4.10, and the mean of NLR in the non-severe group = 7.53 with a standard deviation = 5.18, which is statistically significant. The mean difference between groups was 2.58 (95% CI: 0.313-4.856). Therefore, from the analysis results, it can be concluded that pregnant patients with severe COVID-19 have a higher NLR than patients with mild COVID-19 (see Table 5).

Table 6, shows the test results obtained with a value of p = 0.010). Because the value of p <0.05, the test result was stated to be significant, which means that there is a difference in the median NLR between the dead and living groups. The median NLR in the group that died = 9.49 with a minimum value of 4.27 and a maximum value of 21.44. Meanwhile, the median NLR in the living group = 6.00, with a minimum value of 1.59 and a maximum value of 33.32. Therefore, from the analysis results, it can be concluded that pregnant patients with COVID-19 who died had a higher NLR than patients who did not die (Table 6).

Table 5. NLR Analysis of COVID-19 Severity (analysis using independent-samples t-test)

Variables	n	Mean	SD	p
Severe	27	10.11	4.10	0.026
Non-Severe	55	7.53	5.18	

Table 6. NLR Analysis on Mortality (analysis using Mann-Whitney)

Variables	n	Mean	SD	p
Death	30	9.92	3.94	0.001
Alive	52	7.49	5.32	

DISCUSSION

Pregnancy is one of the risk factors that can increase the severity of COVID-19. This happens because, during pregnancy, women experience immunological and physiological changes that can increase the risk of more severe disease due to respiratory infections (Karimi et al., 2021).

The results of this study suggest a significant relationship between gestational age and the severity of COVID-19. This is related to the immune status during pregnancy. In the third trimester, the development of the fetus begins to complete and towards the birth process so an immune response is activated for the birth process of the baby and the placenta. Immune cells will attack the uterine muscle to create a proinflammatory phase that triggers uterine contractions. Increased proinflamma-

tory cytokines can make the body more susceptible to infectious diseases (Phoswa and Khaliq, 2020).

Data analysis shows that the percentage of neutrophils was higher in the severe COVID-19 category. In line with other studies, an increase in neutrophils in the blood is a feature in severe cases of COVID-19 (deKay et al., 2021). Phagocytic cells such as dendritic cells, macrophages/monocytes, and neutrophils have an essential role in SARS-CoV virus infection (Lagunas-Rangel, 2020). Neutrophils are critical effector cells in the immune system. Neutrophils will look for signs of microbial infection, and when microbes are found, neutrophil cells will respond to kill the invading pathogen (Rosales, 2018).

Lymphopenia occurred in both groups, both the severe and non-severe COVID-19 groups. However, the mean values of lymphocytes in the severe COVID-19 group were lower than those in the non-severe COVID-19 group. In line with previous research, lymphopenia is commonly found in COVID-19 patients, especially in severe cases of COVID-19. Lymphopenia in severe COVID-19 patients is due to various mechanisms, such as direct lymphocyte suppression, lymph node destruction, increased inflammatory cytokines, lymphocyte emergence suppressing lactic acidosis, and SARS-CoV-2 attachment to the angiotensin-converting enzyme-2 (ACE-2) on lymphocytes (Ish et al., 2020).

This study shows positive correlation between NLR (neutrophil-lymphocyte ratio) and COVID-19 severity in pregnant patients and has shown its association in several studies. Consistent with previous studies indicating that the NLR in severe COVID-19 was significantly higher than in non-severe COVID-19 (Yang et al., 2020). In previous studies, patients with severe COVID-19 tended to have lower lymphocyte counts, white blood cell counts, and higher neutrophil-lymphocyte ratios (NLRs). NLR is a systemic infection and inflammation marker and has demonstrated an increased inflammatory response in COVID-19 patients. Neutropenia and lymphocytopenia correlate with disease severity and mortality in COVID-19 (Lagunas-Rangel, 2020; Sukrisman et al., 2021). There is significant neutrophil infiltration in the pulmonary capillaries of COVID-19 patients, especially in patients with acute respiratory distress syndrome (ARDS) (deKay et al., 2021).

Lymphocytes are a type of white blood cell that protects the body's immune system against infectious microorganisms and other foreign substances. These cells include natural killer (NK) cells, T cells (cytotoxic), and B cells (adaptive humoral immunity). NK and T cells are essential in infection control (Koyasu and Moro, 2012). In COVID-19, a decrease in cell count is associated with disease severity. In COVID-19, there is also an increase in the expression of NKG2A, an NK cell inhibitor. An increase in NKG2A prevents NK cells from functioning correctly (Zheng et al., 2020).

Neutrophils comprise 50-70% of white blood cells in healthy adults. During pregnancy, neutrophils increase to 95% of peripheral white blood cells. Neutrophils have a role to play against pro inflammatory stimuli during pregnancy. Previous research comparing NLR in pregnant women with COVID-19 to pregnant women without COVID-19 showed that NLR was higher in pregnant women with COVID-19 (72% of pregnant women with COVID-19 experienced an increase in NLR) (Martha and Utama, 2022).

Several changes occur in the T-helper response (Th1 and Th2) during pregnancy through various mechanisms. This

adaptive mechanism shifts the immune response from pro-inflammatory to anti-inflammatory, increasing HLA-G expression to protect the conceptus and decreasing the immune response to viral infection. Several studies reported that mild COVID-19 in pregnancy did not show significant differences with pregnant women without COVID-19 (Erol Koç et al., 2021).

A high NLR value on the first admission should be a worrying sign of the patient's prognosis. Patients with high NLR levels usually come with symptoms, such as fever, cough, and oxygen saturation <93%, requiring immediate treatment in the ICU. Changes in NLR values as the course of COVID-19 can be reflected as changes in the inflammatory process in line with clinical improvement or worsening (Fuad et al., 2021).

Previous studies reported that COVID-19 infection could have adverse effects on pregnant women, including maternal death, care in the ICU, and the need for oxygen support (Arslan et al., 2022). In this study, the mortality rate was higher in severe COVID-19 patients (86.7%), consistent with previous reports showing the importance of prompt treatment of COVID-19 patients with severe symptoms. NLR assessment is beneficial for the early detection of serious illnesses associated with COVID-19 and prompt therapeutic interventions. NLR is considered a strong predictor and prognosis for shortening the course of the disease, accelerating recovery, and reducing mortality in COVID-19 patients (Kerboua, 2021).

There are several shortcomings in this research. First, comorbidities and complications of pregnancy were not excluded from this study sample. Second, this study did not evaluate the course of NLR changes and disease severity during hospitalization. In addition, most women (82%) were admitted to the hospital in the third trimester, so it was impossible to compare clinical presentations in early and late pregnancy.

In conclusion, this study demonstrates essential clinical findings. Laboratory results, especially NLR, can be used as a predictor for treating COVID-19 patients upon admission. Higher levels of NLR tend to have a poor prognosis and require special attention and treatment. Therefore, screening pregnant women for COVID-19 who come for prenatal visits is important.

AUTHORS CONTRIBUTION

All authors contributed equally to collecting this research data, analyzing it, and writing the manuscript.

ACKNOWLEGDEMENT

None.

FINANCIAL AND SPONSORSHIP

The authors are responsible for all study funding without a grant or any external funding source.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCE

Arslan B, Bicer IG, Sahin T, Vay M, Dilek O, Destegul E (2022). Clinical characteristics and hematological parameters associated with disease severity in COVID-19 positive pregnant women undergoing cesarean section: a single-center experience. J. Obstet. Gynaecol. 48(2): 402-410. doi: 10.11-11/jog.15108.

Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2022). Features, evaluation and treatment coronavirus (COVID-19). StatPearls Publishing. Available at: https://www.ncbi.nlm.-

nih.gov/books/NBK554776/(Accessed: 16 January 2022).

deKay JT, Emery IF, Rud J, Eldridge A, Lord C, Gagnon DJ, May TL, Herrera VLM, et al. (2021). DEspRhigh neutrophils are associated with critical illness in COVID-19. Sci Rep. 11(1): 1–11. doi: 10.1038/s41598-021-01943-7.

Erol Koç EM, Flndlk RB, Akkaya H, Karadağ I, Tokalloğlu EÖ, Tekin ÖM (2021). Comparison of hematological parameters and perinatal outcomes between COVID-19 pregnancies and healthy pregnancy cohort. J. Perinat. Med. 49(2): 141–147. doi: 10.1515/-jpm-2020-0403.

Fuad M, Oehadian A, Prihatni D, Marthoenis M (2021). Neutrophil to lymphocyte ratio and covid-19 symptom-based severity at admission. Althea Med. J. 8(1): 1–6. doi: 10.15850/amj.-v8n1.2255.

Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, Terpos E, Dimopoulos MA (2020). Organ-specific manifestations of covid-19 infection. Int. J. Clin. Exp. Med. 20(4: 493–506. doi: 10.1007/s10238-020-00648-x.

Ish P, Malhotra N, Agrawal S Gupta N (2020). Relative lymphocytosis in COVID-19 a ray of hope. Adv. Respir. Med. 88(3): 287–288. doi: 10.5603/-ARM.a2020.0098.

Karimi L, Makvandi S, Vahedian-Azimi A, Sathyapalan T, Sahebkar A (2021). Effect of COVID-19 on mortality of pregnant and postpartum women: a systematic review and meta-analysis. J. Pregnancy. doi: 10.1155/2021/-8870129.

Kemenkes (2021). Keputusan Menteri Kesehatan Republik Indonesia No Hk.0-1.07/Menkes/5671/2021 tentang Manajemen Klinis Tata Laksana, 3, pp.: 1–106.

Kerboua KE (2021). NLR: A Cost-effective nomogram to guide therapeutic interventions in COVID-19. Immunol. Invest. 50(1): 92–100. doi: 10.1080/-08820139.2020.1773850.

Koyasu S, Moro K (2012). Role of innate lymphocytes in infection and inammation. Front. Immunol. 3: 1–13. doi: 10.3389/fimmu.2012.00101.

Krishnan A, Hamilton JP, Alqahtani SA Woreta TA (2021). COVID-19: An overview and a clinical update. World J. Clin. Cases. 9(1): 8–23. doi: 10.12-998/wjcc.v9.i1.8.

Lagunas-Rangel FA (2020). Neutrophil-to-lymphocyte ratio and lymphocyte-to-c-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A Meta-Analysis. J. Med. Virol. 92(10): 1733–1734. doi: 10.10-02/jmv.25819.

Martha NT, Utama BI (2022). Absolute lymphocyte count and neutrophil lymphocyte ratio in pregnancy confirmed positive for SARS-CoV-2 at Dr. M. Djamil Hospital, Padang, 25, pp.: 49–53.

Phoswa WN, Khaliq OP (2020). Is pregnancy a risk factor of COVID-19? Eur. J. Obstet Gynecol Reprod Biol. 252: 605–609.

Rosales C (2018). Neutrophil: a cell with many roles in inflammation or several cell types? Frontiers in Physiology. 9: 1–17. doi: 10.3389/fphys.2018.00113.

Rothan HA, Byrareddy SN (2020). A framework for five big v's of big data and organizational culture in firms. J. Autoimmun. doi: 10.1016/j.jaut.202-0.102433.

Sukrisman L, Sinto R, Priantono D (2021). Hematologic profiles and correlation between absolute lymphocyte count

and neutrophil/ lymphocyte ratio with markers of inflammation of covid-19 in an indonesian national referral hospital. Int. J. Gen. Med. 14(71): 6919–6924. doi: 10.2147/-IJGM.S337440.

Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, Roggero P, Prefumo F, et al. (2021). Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the intercovid multinational cohort study. JAMA Pediatr. 175(8): 817–826. doi: 10.1001/jamapediatrics.2021.1050.

World Health Organization (2020). Clinical management of COVID-19: interim guidance geneva world health organization 2020.

Yang A-P, Liu J, Tao W, Li H (2020). The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 Patients. Int. Immunopharmacol. doi: 10.1016/j.intimp.2020.106504.

Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z (2020). Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell. Mol. Immunol. 17(5): 533–535. doi: 10.10-38/s41423-020-0402-2.

Zhang Z (2016). Univariate description and bivariate statistical inference: The first step delving into data. Ann. Transl. Med. 4(5). Doi: 10.21037/-atm.2016.02.11.