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**ANALYSIS OF THE COVID-19 SEVERITY BASED ON NLR AND THE MORTALITY RATE OF PREGNANT WOMEN WITH COVID-19 AT RSUD DR. MOEWARDI**

**Dhea Fitria Rachma1), Teguh Prakosa2), Sigit Setyawan3), Abdurahman Laqif2)**

1. Medical Student, Faculty of Medicine, Universitas Sebelas Maret Surakarta
2. Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sebelas Maret Surakarta
3. Department of Parasitology, Faculty of Medicine, Universitas Sebelas Maret Surakarta

**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 in the form of lymphocytes, neutrophils, and NLR are considered prognostic in COVID-19. The purpose of this study was to analyze 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-sectiona*l* using medical record data. The research subjects were 82 pregnant women with confirmed COVID-19 who were taken using the consecutive sampling technique. 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.

**Results:** There was a significant correlation between the severity of COVID-19 based on the number of lymphocytes, neutrophils, and NLR on the mortality rate of pregnant women with COVID-19 (p <0.001, 0.001, and 0.026).

**Conclusion:** Laboratory results, especially NLR can be used as a predictor for the treatment of COVID-19 patients on admission. Higher levels of NLR tend to have a worse prognosis.

**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

**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 “immunocompromised” immune systems, such as those with other underlying infections or chronic illnesses, and pregnant women (Phoswa and Khaliq, 2020).

A report shows that 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 %) of deaths 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 has an impact on hematopoietic and homeostasis. Biomarkers that are 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, using medical record data. The approach used in this research is cross-sectional.

1. **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. 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. The sample size in this study was 82 samples taken by consecutive sampling techniques.

1. **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.

1. **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 (World Health Organization, 2020). 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).

1. **Study Instruments**

Patient medical records from March 2020 to January 2022.

1. **Data analysis**

The characteristics of the study sample were described using the parameters of frequency and percentage. For categorical data, data analysis was performed using the contingency coefficient correlation test. 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.

1. **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 3 patients (3.7%). Based on the number of parities, the majority of patients were multiparas, namely 57 patients (69.5%) and the rest were nulliparas, namely 25 patients (30.5%). Based on BMI, the majority of 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**).

**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/m2) | 5 | 6.1% |
|  | Normal (18.5-25 km/m2) | 38 | 46.3 % |
|  | *Overweight* (>25 km/m2) | 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** |
| 1. | Ages (years) | 30.5 | 6.3 | 19 | 44 |
| 2. | Gestational age (weeks) | 34.7 | 7.3 | 8 | 41 |
| 3. | BMI (kg/m2) | 24.6 | 4.5 | 16.2 | 39.2 |
| 4. | Respiration (x/minute) | 22.6 | 5.3 | 16 | 44 |
| 5. | Temperature (oC) | 36.6 | 0.54 | 36 | 38.6 |
| 6. | Hemoglobin (g/dl) | 11.3 | 1.5 | 6.1 | 14.5 |
| 7. | Total Leukocytes (x103/mm3) | 11.8 | 4.9 | 5 | 26.3 |
| 8. | Platelets (x103/ mm3) | 266.7 | 95.8 | 48 | 575 |
| 9. | Neutrophil (%) | 82.4 | 7.1 | 55 | 93.3 |
| 10. | Lymphocytes (%) | 12.7 | 5.9 | 2.8 | 34.6 |
| 11. | NLR (%) | 8.4 | 4.9 | 1.6 | 33.3 |

1. **Bivariate Analysis**

The bivariate analysis of categorical data used in this study was the contingency coefficient correlation test. Based on table 3, the results of the contingency coefficient correlation analysis between gestational age and the severity of COVID-19 show a correlation contingency coefficient of r = 0.357 which indicates a weak correlation between gestational age and severity but statistically shows a significant correlation with a value of p = 0.02 (p <0.05) (**see Table 3**).

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Non Severe****(n = 55)** | **Severe****(n = 27)** | **rk (*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 | 0.02\* |
| 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 | 0.31 |
| 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 | 0.000\* |
| Death | 4 (13.3%) | 26 (86.7%) |  |  |
| Alive | 51 (98.1%) | 1 (1.9%) |  |  |
| **Clinical Manifestation** |  |  | 0.508 | 0.000\* |
| Asymptomatic | 34 (100%) | 0 (0%) |  |  |
| Symptomatic | 21 (43.8%) | 27 (56.3%) |  |  |

# Note: \*significant at <0.05

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 median of platelets (×103) was 229 in the non-severe group and 289 in the severe group. This shows that patients with severe COVID-19 had a median 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 4. Data analysis (analyzed using independent-samples t-test and Mann-Whitney)**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | **Non Severe** **(n= 55)** | Severe (n= 27) | p-value |
| Age (years), mean + SD | 29.4 **+** 6.6 | 32.7+ **\_** 5.1 | 0.016a\* |
| Gestational age (weeks), median (min-max) | 38 (8-41) | 31 (8-40) | <0.001b\* |
| BMI (kg/m2), median (min-max) | 23.7 (16.2 – 39.2) | 26.8 (18.4 – 35.3) | 0.090 |
| Clinical, median (min-max) |  |  |  |
| Respiratory (x/min) | 20 (16 – 28) | 28 (20 – 44) | <0.001b\* |
| Temperature (oC) | 36.5 (36 – 38.6) | 36.7 (36 – 38.6) | 0.099b |
| Hematological Parameters |  |  |  |
| Hemoglobin (g/dl), mean + SD | 11.4 + 1.3 | 10.9 + 1.8 | 0.111a |
| Total Leukocytes (x103/mm3), median (min-max) | 10.3 (5– 26) | 11.4 (5.4 – 26.3) | 0.152b |
| Platelets (x103/ mm3), median (min-max) | 229 (100 – 482) | 289 (48 – 575) | 0.043b\* |
| Neutrophils (%), mean + SD | 80.6 + 7.6 | 86.1 + 4.2 | 0.001a\* |
| Lymphocytes (%), mean + SD | 14.1 + 6.5 | 9.8 + 3.5 | <0.001a\* |

# Note: at-test, bMann-Whitney, \*significant at <0.05

Based on table 5, the test results are obtained with a value of t = 2.264 and p = 0.026 (p<0.05). Because the p-value <0.05, the test results were declared significant, which means that 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 results of the analysis, it can be concluded that pregnant patients who have severe COVID-19 have a higher NLR than patients who have mild COVID-19 (**see Table 5**).

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **n** | **Mean + SD** | **Difference (95% CI)** | **t** | **P** |
| **Severe** | 27 | 10.11 + 4.10 | 2.58 (0.313-4.856) | 2.264 | 0.026\* |
| **Non-Severe** | 55 | 7.53 + 5.18 |

# Note: \*significant at <0.05

Based on table 6, the test results were obtained with a value of u = 437 and p = 0.01 (p <0.05). 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 medianNLR 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 results of the analysis, it can be concluded that pregnant patients with COVID-19 who died had a higher NLR than patients who did not die (**see Table 6**).

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **n** | **Median (Minimum-Maximum)** | **U** | **p** |
| **Death** | 30 | 9.49 (4.27-21.44) | 437 | 0.01\* |
| **Alive** | 52 | 6.00 (1.59-33.32) |

# Note: \*significant at <0.05

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

Based on data analysis, the percentage of neutrophils was found to be 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 important role in SARS-CoV virus infection (Lagunas-Rangel, 2020). Neutrophils are important 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 gives the result that there is a 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 marker of systemic infection and inflammation 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). Both NK cells and T cells play important roles in infection control (Koyasu and Moro, 2012). In COVID-19, a decrease in cell count is associated with disease severity. In addition to the reduction in T cells, NK cells, and CD8+, 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 properly (Zheng et al., 2020).

Neutrophils make up 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 found to be higher in pregnant women with COVID-19 (72% of pregnant women with COVID-19 experienced an increase in NLR) (Martha and Utama, 2022).

During pregnancy, several changes occur in the T-helper response (Th1 and Th2) through various mechanisms. This adaptive mechanism shifts the immune response from a pro-inflammatory state to an anti-inflammatory state which contributes to increasing HLA-G expression to protect the conceptus as well as 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 can 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 who present with severe symptoms. NLR assessment is very helpful for the early detection of serious illnesses associated with COVID-19 and for 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, the majority of women (82%) were admitted to the hospital in the third trimester, therefore it was not possible to compare clinical presentations in early and late pregnancy.

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

**AUTHORS CONTRIBUTION**

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

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**CONFLICT OF INTEREST**

There are no conflicts of interest.

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