The Severity of COVID-19 and its Correlation with Inflammation Biomarkers

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Abstract

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 has been spread quickly and caused 5 million deaths until February 2022. Severe symptoms of the infection may lead to death that prompts appropriate clinical diagnosis and adequate treatment going to be necessary. COVID-19 shows a severe inflammatory response which causes an imbalance in the immune response. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients.

AIM: The purpose of this study was to discover the role of neutrophil-lymphocyte ratio (NLR), neutrophil-monocyte ratio (NMR), and lymphocyte-monocyte ratio (LMR) as inflammatory biomarkers for the severity of COVID-19.

METHODOLOGY: This study is a single-center retrospective cohort study. The sample of this study was taken by consecutive sampling with complete clinical data from 1035 patients from Andalas University Teaching Hospital from April 2020 to September 2021. This study used SPSS Version 25.0 for data management and analysis.

RESULTS: There was a relationship between the degree of COVID-19 infection and the NLR value (p = 0.001), as well as the LMR (p = 0.001), NMR (p = 0.001), and ANC (p = 0.001). There was no relationship between the degree of COVID-19 infection and the NMR value (p = 0.001), as well as the LMR (p = 0.001), NMR (p = 0.001), and ANC (p = 0.001).

CONCLUSION: The severity of COVID-19 symptoms could be predicted through inflammatory biomarkers such as NLR, LMR, and NMR.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 was first reported in Wuhan, China, on December 31, 2019. This incident quickly spread throughout the world and the World Health Organization has declared it a pandemic [1]. According to the WHO data on February 25, 2022, there are 428,511,601 cases have been confirmed worldwide, with 5,911,081 deaths [2]. Severe symptoms of COVID-19 can cause pneumonia, ARDS, multiorgan failure, and even death, the highest mortality occurs in patients with pre-existing chronic diseases [3].

The Severity of COVID-19 patients categorized according to symptoms and assessment from doctors. Pneumonia symptoms, SpO2 levels, respiratory rate, and chest imaging are required for confirmation. Most people have fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), and myalgia (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhea, nausea, and vomiting, have also been reported. Moderate symptoms are characterized by pneumonia like symptoms with increased respiratory rate and SpO2 above 90%. Meanwhile severe symptoms showed by severe pneumonia with SpO2 below 90%. Patients with none of those conditions belong to mild symptoms. Severe symptoms are characterized by symptoms of severe pneumonia and SpO2 below 90% [4]. Due to the rapid spread of COVID-19 and the potential for COVID-19 to become a serious disease, prompt clinical diagnosis and treatment development are required. Analysis of laboratory findings and clinical
symptoms can be carried out in cases of COVID-19 where there is severe inflammation so that certain biomarkers will increase.

Inflammatory lung disease caused by bacterial or viral pneumonia may have different immune response with Covid-19. In every inflammation, the body’s response will be as compensation, but in COVID-19, symptoms of a severe inflammatory response are found, which causes a weak adaptive immune response, resulting in an imbalance in the immune response. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients. Neutrophil-to-lymphocyte ratio (NLR) has been widely studied as a prognostic biomarker against pneumonia, Takayasu, thyroiditis, and tumor disease [5], [6], [7]. NLR, neutrophil-to-monocyte ratio (NMR), and lymphocyte-monocyte ratio (LMR) as biomarkers of inflammation need to be studied to determine the relationship with COVID-19 severity degree. This study aims to know the role of these biomarkers in the severity of COVID-19 and the correlation of the biomarkers to other factors.

Patients and Methods

Patients

This study is a single-center retrospective study, on clinical characteristics and laboratory data of confirmed COVID-19 patients with cohort validation. The sample of this study was taken by consecutive sampling with complete clinical data from 1035 subjects with symptoms of COVID-19 all of these patients were patients who were treated at the Andalas University Teaching Hospital from April 2020 to September 2021. RT-PCR examination was performed and found 893 patients with a positive result and 142 patients were confirmed negative. The diagnostic criteria used are the results of the RT-PCR examination on patients who enter the Laboratory of the Diagnostic and Research Center for Infectious Diseases at Andalas University for diagnostics using RT-PCR. Epidemiological data, vital signs, clinical symptoms, comorbidities, and laboratory findings including biochemistry, routine blood, and chest radiograph were taken at the onset of COVID-19 infection. Data were obtained from medical records and information from patients and their families.

Results

Demographics and clinical characteristics

Form 1035 patients with clinical manifestation of COVID-19 in Andalas University Hospital, RT-PCR examination was performed and found 893 patients with a positive result and 142 patients were confirmed negative. A list of demographic and clinical characteristics of COVID-19 infection is shown in Table 1. COVID-19 confirmed cases from 893 patients were categorized into mild, moderate, and severe groups based on the WHO criteria. The most dominant is mild group 597 (66.85%) followed by moderate group 223 (24.97%) and severe group 73 (8.17%). The major age of each categorized group range from 56 to 65 years old, mild 151 (25.29%), moderate 48 (21.52%), and severe 19 (26.02%). Male tended to be confirmed more positive than the female from each group mild 241 (40.36%), moderate 116 (52.01%), and severe 41 (56.16%). Symptoms from the patient are different from each criteria, severe criteria mostly come with shortness of breath (87.67%) followed closely by cough (86.3%). Moderate criteria have a cough (82.9%) as the dominant symptom and fever (71.3%), whereas mild is likely to come with fever (64.3%) and cough (59.9%). Hypertension is the main comorbid in each group mild (64.16%), moderate (61.53%), and severe (46.29%) followed by diabetes mellitus type 2.
In patients with negative PCR results (n = 142) data in Table 3, there was no significant relationship between the degree of infection and the NLR value (p = 0.144), the degree of infection with the LMR value (p = 0.700), and the degree of infection with NMR (p = 0.120).

### Discussion

This study involved 893 patients infected with COVID-19 clinical characteristics and laboratory peer analysis. Compared with the group with mild symptoms, the group with severe symptoms was mostly older patients, most had a high fever and had at least one underlying comorbid illness. The clinical findings of COVID-19 patients are mostly in line with the previous studies. These findings suggest that older people and chronic illnesses are more likely to be infected with COVID-19 [8]. Sixty years old, hypertension, diabetes mellitus, chronic kidney/lung/liver disease, cancer, and smoking are risk factors for COVID-19 disease [9, 10].

Identification of risk factors is important for patients with severe symptoms for appropriate supportive care or access to the ICU when necessary. Severe cases show lower lymphocyte counts and higher neutrophil levels. Severe clinical conditions showed an increase in several biomarkers of infection. As a widely used factor for systemic infection and inflammation, NLR is used to assess disease severity and clinical prognosis of pneumonia [5]. The highest average number of NLRs was found in COVID-19 patients who died. In a study consistent with the results of this study, Yang et al. in Wuhan increased NLR and age was associated with the severity of COVID-19 symptoms. Results binary logistic regression showed an increase in NLR (hazard risk [HR] 2.46, with 95% confidence interval [CI] 1.98–4.57) and age (HR 2.52, 95% CI 1.65–4.83) as an independent factor for poor clinical outcome in COVID-19. The study also found that the ratios of NLR, LMR, PLR, and CRP were statistically significantly higher in severe patients [11]. The progression of COVID-19 disease to severe symptoms is thought to be the result of viral infection and damage from cytokine storms [12]. Other hypotheses stated that

### Laboratory finding

The result of the blood test of the patients in the hospital is shown in Table 2. Hemoglobin count is not significantly different between each group (p = 0.139). Meanwhile, leukocyte is significantly higher in severe cases than in mild and moderate cases (8200 vs. 6500, p = 0.006). The severe group also has an absolute neutrophil count higher than the mild and moderate (6,603/mcL vs. 3,990/mcL and 4,350/mcL, respectively, p = 0.001). Contrary absolute lymphocyte count is lower in severe cases as compared to mild and moderate groups (1,056/mcL vs. 1,358/mcL and 1,802/mcL, respectively, p = 0.001). Comparison between neutrophil, lymphocyte, and monocyte by NLR, LMR, and the severe group significantly has NLR and NMR higher than the mild and moderate group (6.91 vs. 2.07 and 3.13, p = 0.001 and 13.67 vs. 7.86 and 9 (p = 0.001), respectively. Compared with mild and moderate cases, most patients in the severe group showed a lower level of LMR (2.2 vs. 3.67 and 3, p = 0.001). No significant differences in absolute monocyte count and hemoglobin were found.

![Open Access Maced J Med Sci. 2022 May 27; 10(A):911-915.](image-url)
the occurrence of lymphopenia in COVID-19 patients with severe symptoms was due to lymphocytic infiltration into pulmonary tissue induced by local inflammation and pyroptosis of infected cells [13]. Lymphocyte count and lymphopenia may serve as a rapid tool that can quickly identify COVID-19 patients with more severe clinical presentation. The previous studies observed that lymphopenia is a common observation in patients with the severe acute respiratory syndrome (SARS) caused by SARS infection may either directly suppress bone marrow or induce immune-mediated destruction of lymphocytes resulting in lymphopenia. SARS-CoV-2 might share a similar inner mechanism with the SARS virus, including direct infection and destruction of lymphocytes [14].

Research by Zhang et al. in Wuhan showed an increase in neutrophils in patients with COVID-19 [15]. In a study by Sadigh et al. on 78 peripheral blood smears of COVID-19 patients, a granulocytocreaction with immaturity, dysmorphism, and apoptotic degenerative morphology was observed when hospitalization in patients with COVID-19, they observed that neutrophil smudges were significantly increased in COVID-19 patients compared to the control group [16]. Research conducted by Erdogan et al., showed no statistically significant difference in the LMR values of patients with mild COVID-19 symptoms and weight, but there were statistical differences in the NLR, PLR, and LCR variables [17]. A study by Sun et al. showed that there was a significant difference in monocyte count, and disease severity between COVID-19 patients and the control group. They demonstrated that the monocyte-lymphocyte ratio (MLR) was higher in COVID-19 patients than in the control group, especially in patients with severe COVID-19 [18].

Anurag et al. study, older age, higher total leukocyte count, neutrophilia, lymphopenia, eosinopenia, high NLR, and high NMR are associated with severe COVID-19 [19]. According to some current evidence, neutrophil count determines the prognosis of severe COVID-19 and also plays an important role in the immunopathology of severe COVID-19. In addition, increased neutrophil counts (by cytokines such as granulocyte colony-stimulating factor (G-CSF)), neutrophil recall, and their inflammatory activity as well as neutrophil extracellular traps from overactive neutrophils may be responsible for severe complications of COVID-19, including ARDS. This raises the question of whether neutrophil microparticles are involved in COVID-19-related complications. Microparticles, also known as extracellular vesicles, are particles with a diameter of 30–1000 nm, which are released from various cells under physiological and pathological conditions. These particles play an important role in the development and progression of various diseases [20].

### Conclusion

Most of the degrees of COVID-19 infected were mild degrees as many as 597 people with an NLR average value of 2.07 (0.27–34.50), an NMR average value of 7.86 (3–46), an LMR average value of 3.67 (0.25–25), an ANC value of 3.990 (945–45). There was a relationship between the degree of COVID-19 infection and the NLR value (p = 0.001), as well as the LMR (p = 0.001), NMR (p = 0.001), and ANC (p = 0.001).

Most of the degrees of infection in patients with negative PCR results were moderate degrees as many as 70 people with a mean NLR value of 9.0694 (0.51–47.50), a mean NMR value of 18.6199 (1.15–47.50), and a mean LMR was 3.0324 (0.29–19.50), the ANC value of 3.990 (945–45). There was no relationship between the degree of infection in the negative PCR patient group and the NLR value (p = 0.144), as well as the LMR (p = 0.700), NMR (p = 0.120), and ANC (p = 0.90).

### Recommendations

Biomarker is mandatory to investigate of the suspect case of COVID-19.

### References

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