Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 27; 10(A):911-915.
https://doi.org/10.3889/oamjms.2022.9639
eISSN: 1857-9655
Category: *A - Basic Sciences*
Section: *Immunology*

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

Beni Indra[1]*, Nur Indrawaty Lipoeto[2], Hardisman Hardisman[3], Andani Eka Putra[4], Djong Hon Tjong[5], Sukri Rahman[6], Elfira Yusri[7], Muhammad Ridho Bilhaq[8], Yusan Pratama[8], Yudha Risman[8]

[1]Department of Anesthesiology, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia; [2]Department of Nutrition, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia; [3]Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia; [4]Department of Microbiology, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia; [5]Department of Biology, Faculty of Mathematics and Natural Science, Universitas Andalas, Padang, West Sumatera, Indonesia; [6]Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia; [7]Department of Clinical Pathology, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia; [8]Senior Clerkship, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia

Edited by: Slavica Hristomanova-Mitkovska
Citation: Indra B, Lipoeto NI, Hardisman H, Putra AE, Tjong DH, Rahman S, Yusri E, Bilhaq MR, Pratama Y, Risman Y. The severity of COVID-19 and its Correlation with Inflammation Biomarkers. Open-Access Maced J Med Sci. 2022 May 27; 10(A):911-915. https://doi.org/10.3889/oamjms.2022.9639
Keyword: COVID-19; Neutrophil-to-lymphocyte ratio; Neutrophil-to-monocyte ratio; Lymphocyte-to-monocyte ratio; Biomarkers
***Correspondence:** Beni Indra, Department of Anesthesiology, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia.
E-mail: beniindra@med.unand.ac.id
Received: 08-Apr-2022
Revised: 10-May-2022
Accepted: 17-May-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

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 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 ($p = 0.90$).

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 categotized 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 respon 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 with clinical symptoms of COVID-19 and who come for an examination because there is a history of contact with COVID-19 patients, as well as patients who have a history of traveling out of town. Clinical manifestations include fever, with or without respiratory symptoms, and chest X-ray of pneumonia. The etiology of the cause was confirmed by RT-PCR on a respiratory swab sample and positive for COVID-19 virus RNA was found.

Clinical characteristics and laboratory data

All results of the COVID-19 infection screening were taken from respiratory swabs taken when the patient was admitted to treatment, the samples were sent to 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.

Statistical analysis

This study uses SPSS version 25.0 for data management and analysis. The distribution of the data was abnormal after being tested by Kolmogorov–Smirnov analyst. Kruskal–Wallis non-parametric test was used to analyze the association between NLR, NMR, LMR, and group of the severity of the patient.

Ethical consideration

This research involves humans as research subjects. The ethical implications of this research follow the provisions of the Declaration of Helsinki and have passed the ethical test from the ethics committee of the Faculty of Medicine, Universitas Andalas Padang, with number 552/UN.16.2/KEP-FK/2022. All medical matters relating to this research are confidential. Research subjects have the right to refuse to participate in the study if they do not agree.

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.

Table 1: Demographic data of the study

Patient characteristic	f (%), n = 893 (%)	Mild, n = 597	Moderate, n = 223	Severe, n = 73	p
Age (years)					0.716
Childhood (<19th)	34 (3.8)	21 (3.5)	12 (5.38)	1 (1.3)	
Teenagers (19–25th)	121 (13.54)	83 (13.9)	29 (13)	9 (12.32)	
Early adult (25–35th)	145 (16.23)	96 (16.08)	39 (17.48)	10 (13.69)	
Late adult (36–45th)	93 (10.41)	65 (10.88)	19 (8.5)	9 (12.32)	
Early elderly (46–55th)	160 (17.91)	106 (17.75)	38 (17.04)	16 (21.91)	
Middle elderly (56–65th)	218 (24.41)	151 (25.29)	48 (21.52)	19 (26.02)	
Late elderly (>65th)	122 (13.66)	75 (12.56)	38 (17)	9 (12.32)	
Gender					0.001
Man	398 (44.56)	241 (40.36)	116 (52.01)	41 (56.16)	
Woman	495 (55.43)	356 (59.63)	107 (47.98)	32 (43.83)	
Symptom					
Fever	601 (67.3)	384 (64,3)	159 (71.30)	58 (79.4)	0.012
Cough	602 (67.413)	354 (59.29)	185 (82.9)	63 (86.3)	0.001
Malaise	153 (17.133)	87 (14.57)	46 (20.6)	20 (27.4)	0.007
Takayasu	329 (36.84)	116 (19.43)	149 (66.8)	64 (87.67)	0.001
Vomiting	145 (16.23)	85 (14.2)	49 (21.97)	11 (15)	0.025
Anosmia	267 (29.89)	207 (34.67)	51 (22.86)	9 (12.3)	0.001
Decreased appetite	102 (11.42)	58 (9.7)	30 (13.4)	14 (19.1)	0.031
Sore throat	98 (10.97)	70 (11.7)	18 (8)	10 (13.69)	0.244
Headache	74 (8.2)	52 (8.7)	18 (8)	4 (5.4)	0.634
Myalgia	17 (1.9)	9 (1.5)	7 (3.1)	1 (1.3)	0.296
Diarrhea	47 (5.2)	22 (3.68)	23 (10.3)	2 (2.7)	0.001
Stomach pain	72 (8.6)	46 (7.7)	21 (9,4)	5 (6.8)	0.673
Comorbid					0.037
Hypertension	208 (60.46)	111 (64.16)	72 (61.53)	25 (46.29)	
Diabetes mellitus	79 (22.96)	38 (21.96)	26 (22.22)	15 (27.77)	
Cardiovascular disease	15 (4.36)	7 (4.04)	6 (5.12)	2 (3.7)	
Cerebrovascular disease	3 (0.87)	1 (0.57)	0	2 (3.7)	
Kidney disease	10 (2.9)	4 (2.3)	4 (3.4)	2 (3.7)	
Respiratory disease	22 (6.39)	10 (5.78)	4 (3.4)	8 (14.814)	
Carcinoma	7 (2.03)	2 (1.15)	5 (4.27)	0	

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 groups than in 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 shown 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.

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 analysis 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

Table 2: Laboratory finding of group RT-PCR positive

	f (%), n = 893	Mild, n = 597	Moderate, n = 223	Severe, n = 73	p
Routine blood					
Hb (g/dl)	13.3 (3.8–18.5)	13.4 (6–18.5)	13.4 (6.3–18)	13 (3.8–17.2)	0.139
Leukocytes (/µl)	6600 (2100–22900)	6500 (2100–17600)	6500 (2100–19300)	8200 (2600–22900)	0.006
Platelets (/µl)	245000 (20000–698000)	251000 (39000–628000)	226000 (20000–698000)	225000 (104000–570000)	–
Basophil (%)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	–
Eosinophil (%)	2 (0–6)	2 (0–6)	2 (0–5)	1 (1–4)	0.257
Rod neutrophil (%)	1 (0–20)	1 (0–20)	1 (0–4)	2 (0–4)	0.001
Segmental neutrophil (%)	64 (20–92)	60 (30–90)	67 (20–90)	77 (46–92)	0.001
Lymphocytes (%)	26 (2–74)	30 (2–74)	22 (3–60)	12 (2–42)	0.001
Monocytes (%)	8 (2–30)	8 (2–14)	8 (2–30)	6 (2–12)	0.001
AMC (/mcL)	486 (52–2490)	495 (66–1368)	464 (90–2490)	480 (52–1716)	0.576
NMR	8.37 (1.05–47.5)	7.86 (3–46)	9 (1.05–47)	13,67 (4.58–47.5)	0.001
LMR	3.4 (0.25–25)	3.67 (0.25–25)	3 (0.33–16.5)	2.2 (0.5–9)	0.001
ANC (/mcL)	4148 (420–20152)	3.990 (945–14.608)	4350 (420–18048)	6603 (1564–20152)	0.001
ALC (/mcL)	1620 (52–11804)	1.802 (128–11.804)	1358.5 (153–3760)	1056 (52–6975)	0.001
NLR	2.5 (27–47.5)	2.07 (0.27–34.50)	3.13 (0.33–31.33)	6.91 (1.1–47.5)	0.001

AMC: Absolute monocyte count, NMR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NLR: Neutrophil-to-lymphocyte ratio.

Table 3: Laboratory finding in negative PCR group

	f (%), n = 142	Mild, n = 34	Moderate, n = 70	Severe, n = 38	p
Routine blood					
Hb (g/dl)	12.2 (3.1–17.1)	12.3 (3.1–17.0)	12.0 (6.0–15.9)	12.4 (6.3–17.1)	0.540
Leukocytes (/µl)	12,085 (2,100–40,900)	10.938 (2,500–29,100)	11,925 (3,300–40,900)	13,404 (2,100–29,400)	0.127
Platelets (/µl)	292,514 (19,000–813,000)	277,676 (19,000–622,000)	290,900 (49,000–763,000)	308,763 (55,000–813,000)	–
Basophil (%)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	–
Eosinophil (%)	1 (0–4)	1 (0–3)	1 (0–4)	1 (0–3)	0.358
Rod neutrophil (%)	2 (0–11)	2 (0–4)	2 (0–11)	3 (0–8)	0.103
Segmental neutrophil (%)	74 (32–92)	72 (32–92)	74 (37–90)	77 (53–92)	0.113
Lymphocytes (%)	15 (2–63)	18 (2–63)	22 (3–60)	14 (3–33)	0.186
Monocytes (%)	5 (2–60)	5 (2–12)	8 (2–30)	7 (2–60)	0.214
AMC (/mcL)	627 (82–4,140)	522 (106–1,416)	464 (90–2490)	672 (150–4,140)	0.275
NMR	18.61 (1.15–47.5)	17.7 (4.7–47.5)	9 (1.05–47)	17.38 (1.15–46.0)	0.120
LMR	3.03 (0.29–19.5)	3.7 (1.0–19.5)	3 (0.33–16.5)	2.8 (0.3–15.0)	0.700
ANC (/mcL)	9,769 (1,088–37,219)	8,745 (1,088–26,160)	4350 (420–18048)	9,555 (1,702–37,219)	0.090
ALC (/mcL)	1,471 (189–5,066)	1,415 (380–3,510)	1358.5 (153–3760)	1,501 (414–4,496)	0.552
NLR	9.06 (0.51–47.50)	8.89 (0.51–47.50)	3.13 (0.33–31.33)	7.6 (1.28–30.33)	0.144

AMC: Absolute monocyte count, NMR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NLR: Neutrophil-to-lymphocyte ratio.

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 granulocytic reaction 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 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 was 9769.73 (1.088–37,219). 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

1. World Health Organizations. COVID-19-China. Geneva: World Health Organization; 2020. Available from: https://www.who.int/

emergencies/disease-outbreak-news/item/2020-DON233 [Last accessed on 2022 Jan 22].

2. World Health Organizations. WHO Coronavirus (COVID-19) Dashboard. Geneva: World Health Organizations; 2022. Available from: https://www.covid19.who.int/table [Last accessed on 2022 Feb 25].
3. Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. Gac Sanit. 2021;35:530-2. https://doi.org/10.1016/j.gaceta.2021.10.085
   PMid:34929892
4. World Health Organizations. Living Guidance for Clinical Management of COVID-19. Geneva: World Health Organizastions; 2021. p. 63. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1 [Last accessed on 2021 Nov 23].
5. Lee H, Kim I, Kang BH, Um SJ. Prognostic value of serial neutrophil-to-lymphocyte ratio measurements in hospitalized community-acquired pneumonia. PLoS One. 2021;16(4):0250067. https://dx.doi.org/10.1371/journal.pone.0250067
   PMid:33857241
6. Pan L, Du J, Li T, Liao H. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio associated with disease activity in patients with takayasu's arteritis: A case-control study. BMJ Open. 2017;7(4):014451. https://doi.org/10.1136/bmjopen-2016-014451
   PMid:28473512
7. Keskin H, Kaya Y, Cadirci K, Kucur C, Ziypak E, Simsek E, *et al.* Elevated neutrophil-lymphocyte ratio in patients with euthyroid chronic autoimmune thyreotidis. Endocr Regul. 2016;50(3):148-53. https://doi.org/10.1515/enr-2016-0017
   PMid:27560798
8. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T*, et al*. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect. 2020;80(6):656-65. https://doi.org/10.1016/j.jinf.2020.03.041
   PMid:32283155
9. Jordan RE, Adab P, Cheng KK. Covid-19: Risk factors for severe disease and death. BMJ. 2020;368:1198. https://doi.org/10.1136/bmj.m1198
   PMid:32217618
10. Ministry of Health and Family Welfare. Clinical Management Protocol for COVID-19. Vol. 12. New Delhi: Ministry of Health and Family Welfare; 2016. p. 754-7.
11. Yang AP, Liu JP Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504. https://doi.org/10.1016/j.intimp.2020.106504
    PMid:32304994
12. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, *et al.* Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763. https://doi.org/10.1016/j.ebiom.2020.102763
    PMid:32361250
13. Wang Y, He Y, Tong J, Qin Y, Xie T, Li J, *et al.* Characterization of an asymptomatic cohort of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected individuals outside of Wuhan, China. Clin Infect Dis. 2020;71(16):2132-8. https://doi.org/10.1093/cid/ciaa629
    PMid:32442265
14. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Deng Y, *et al.* Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. Int J Infect Dis. 2020;96:131-5. https://doi.org/10.1016/j.ijid.2020.04.086
    PMid:32376308
15. Zhang L, Huang B, Xia H, Fan H, Zhu M, Zhu L, *et al.* Retrospective analysis of clinical features in 134 coronavirus disease 2019 cases. Epidemiol Infect. 2020;148:199. https://doi.org/10.1017/s0950268820002010
    PMid:32878654
16. Sadigh S, Massoth LR, Christensen BB, Stefely JA, Keefe J, Sohani AR. Peripheral blood morphologic findings in patients with COVID-19. Int J Lab Hematol. 2020;42(6):248-51. https://doi.org/10.1111/ijlh.13300
    PMid:32730694
17. Erdogan A, Can FE, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients. J Med Virol. 2021;93(9):5555-9. https://doi.org/10.1002/jmv.27097
    PMid:34019701
18. Sun S, Cai X, Wang H, He G, Lin Y, Lu B, *et al.* Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta. 2020;507:174-80. https://doi.org/10.1016/j.cca.2020.04.024
    PMid:32339487
19. Anurag A, Jha PK, Kumar A. Differential white blood cell count in the COVID-19: A cross-sectional study of 148 patients. Diabetes Metab Syndr Clin Res Rev. 2020;14(6):2099-102. https://doi.org/10.1016/j.dsx.2020.10.029
    PMid:33160224
20. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, *et al.* Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med. 2020;217(6):20200652. https://doi.org/10.1084/jem.20200652
    PMid:32302401