ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2021, Volume 10, Number 2: 653-658
P-ISSN.2089-1180, E-ISSN: 2302-2914

Bali Medical Journal
www.BaliMedicalJournal.org
Published by Bali Medical Journal

The correlation of neutrophil-to-lymphocyte ratio (NLR) and monocytes-to-lymphocytes ratio (MLR) with disease severity in hospitalized patients with Coronavirus disease 2019 (COVID-19)

Suhartono[1*], Indra Wijaya[2], Nadjwa Zamalek Dalimoenthe[3]

[1]Department of Internal Medicine, Dr. Pirngadi General Hospital, Medan, Indonesia;
[2]Division of Hematology-Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin Hospital Bandung, Indonesia;
[3]Department of Clinical Pathology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin Hospital Bandung, Indonesia;

*Corresponding author:
Suhartono;
Department of Internal Medicine, Dr. Pirngadi General Hospital, Medan, Indonesia;
suhartono2604@gmail.com

Received: 2021-04-29
Accepted: 2021-07-16
Published: 2021-07-30

ABSTRACT

Background: Early intervention of cases with potential progression to severe disease is essential to improve survival probability in Coronavirus disease 2019 (COVID-19). Systemic inflammation plays an essential role in the process of disease aggravation. This study aimed to assess the correlation of systemic inflammatory response related biomarkers neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) on time to admission with the disease severity of inpatients with COVID-19.

Methods: We performed a retrospective study using secondary data from medical records of inpatients with COVID-19 at Murni Teguh Memorial Hospital, Medan, Indonesia, from June 1 to September 30, 2020. The demographic data were collected from the medical record and the hematologic parameter from the laboratory. NLR and MLR were calculated by dividing the absolute neutrophils and monocytes counts by the absolute lymphocyte counts. The data were tabulated and analyzed by univariate and bivariate analysis with a significance level of $p<0.05$.

Results: Study subjects consisted of 55 non-severe cases and 40 severe cases. The median NLR and MLR of severe and non-severe groups were 7.65 vs 2.92 ($p<0.001$) and 0.46 vs 0.25 ($p=0.013$). The correlation coefficients of NLR and MLR with disease severity were 0.564 ($p<0.001$) and 0.257 ($p=0.012$). The AUC of ROC analysis was 0.830 (cut-off:>4.81;$p<0.001$) in NLR and 0.650 (cut-off:>0.31; $p=0.013$) in MLR to predict the severe disease.

Conclusion: NLR and MLR had a significant positive correlation with the disease severity. NLR is better than MLR in predicting severe disease in hospitalized patients with COVID-19.

Keywords: NLR, MLR, disease severity, COVID-19.
Cite This Article: Suhartono., Wijaya, I., Dalimoenthe, N.Z. 2021.The correlation of neutrophil-to-lymphocyte ratio (NLR) and monocytes-to-lymphocytes ratio (MLR) with disease severity in hospitalized patients with Coronavirus disease 2019 (COVID-19). *Bali Medical Journal* 10(2): 653-658. DOI: 10.15562/bmj.v10i2.2434

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection is a significant health problem facing the world community since early 2020. This disease is highly contagious and has a broad spectrum of clinical manifestations. The clinical features range from asymptomatic respiratory infection to severe pneumonia and the critically ill. Most cases presented with mild to moderate infection in the early days, and approximately 20% progressed rapidly to severe disease accompanied by multisystemic failure that can lead to a patient's death.[1]

There are no specific antiviral agents for the management of COVID-19 that have been presented. The World Health Organization (WHO) recommended supportive therapy that relieves the symptoms and maintains many organs for severe and critical diseases.[2] Severe cases are challenging to treat and have a high mortality rate. Therefore, supportive intervention in severe diseases is consistently not adequate to prevent acute diseases and mortality.[3] Sun et al. reports lower mortality of COVID-19 by early recognition and intervention of critically ill patients in Jiangsu province. Early identification of cases with potential rapid progression to severe disease could facilitate appropriate supportive care and optimize limited healthcare resource allocation.[4]

Previous studies have shown that neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) in blood routine parameters have specific clinical application values in predicting the progress of infectious diseases.[4,5] Several studies about COVID-19 showed abnormal parameters of neutrophils, lymphocytes and monocytes in the peripheral blood of some patients.[6,7] The current study aimed to investigate the correlation of NLR and MLR at admission with disease severity of hospitalized patients with COVID-19

to reveal a potentially helpful predictive factor to disease severity.

METHODS

Study design and participants

This study was a retrospective study among laboratory-confirmed cases with COVID-19 at Murni Teguh Memorial Hospital, Medan, Indonesia, from June 1 to September 30, 2020. The subjects enrolled with total sampling of inpatients at isolation wards aged 18 years or older. Subjects on hemodialysis, cancer treatment, corticosteroid treatment, and history with hematological diseases were excluded from the study. The severity of the disease was classified into non-severe cases (mild and moderate symptoms) and severe cases (severe symptoms and critical illness) based on the severity of symptoms according to the interim guidance of the

Table 1. Characteristics of research subjects

Variables	Disease Severity		p-value
	Non-severe (n= 55)	Severe (n = 40)	
Age, Mean ± SD, years	47 ± 15	57 ± 12	0,001[a]*
Sex, n (%)			
Male	29 (52,7)	29 (72,5)	0,051[c]
Female	26 (47,3)	11 (27,5)	
Illness onset to admission, Median (IQR), days	5 (2 – 9)	7 (2 – 12)	0,001[b]*
Comorbidity, n (%)	24 (46,6)	28 (70)	0,011[c]*
Hypertension	15 (27,3)	15 (37,5)	0,290[c]
Diabetes	10 (18,2)	14 (35,0)	0,063[c]
Cardiovascular disease	3 (5,5)	5 (12,5)	0,275[d]
Malignancy	1 (1,8)	2 (5,0)	0,571[d]
Hepatitis	0 (0,0)	1 (2,5)	0,421[d]
Cerebrovascular disease	0 (0,0)	1 (2,5)	0,421[d]
Hospitalization days, Median (IQR)	12 (7 – 25)	14 (5 – 26)	0,370[b]
Clinical outcomes, n (%)			
Survivor	55 (100)	17 (42,5)	<0,001[d]*
Non-survivor	0 (0,0)	23 (57,5)	

Note: Data are presented as mean ± standard deviation (SD), n (%) and median (IQR). P-values comparing severe and non-severe cases are derived from [a]t test, [b]Mann-Whitney U test, [c]chi-square test, and [d]Fisher's exact test.
Abbreviations: IQR, interquartile range. Significant differences are marked by *

Table 2. Laboratory finding on admission

Variable	Disease Severity		*p*-value
	Non-severe (n = 40)	Severe (n = 55)	
Haemoglobin (g/l)	14,0 ± 1,6	13,8 ± 1,4	0,635[a]
Platelets (x10^9/l)	222 (96 – 498)	199 (95 – 527)	0,186[b]
Leucocytes(x10^9/l)	6,45 ± 2,00	6,99 ± 2,40	0,235[a]
Neutrophil percentage	66,3 (5,4 – 90,1)	83,4 (46,0 – 94,1	< 0,001[b]*
Lymphocyte percentage	24,2 (6,2 – 40,7)	11,0 (1,6 – 39,7)	< 0,001[b]*
Monocyte percentage	8,2 ± 2,9	6,4 ± 3,8[+]	0,008[a]*
Neutrophils/L	3.894 (1.903 – 9.100)	5.579 (1.329 – 11.301)	0,002[b]*
Lymphocytes/L	1.401 ± 581	785 ± 340	< 0,001[a]*
Monocytes/L	483 (151 – 1125)	361 (87 – 1.463)	0,005[b]*
NLR	2,92 (1,22 – 13,98)	7,65 (1.16 – 57,81)	<0,001[b]*
MLR	0,36 (0,05 – 1,78)	0,46 (0,10 – 2,31)	0,013[b]*
CRP (mg/l)	11 (4 – 137)	97 (6 – 160)	< 0,001*

Note: Data are presented as mean ± standard deviation (SD), n (%) and median (interquartile range). *P* values are derived from [a]t test and [b]Mann-Whitney U test. Significant differences are marked by * ($P < 0.01$).
Abbreviations: NLR, neutrophils-to-lymphocytes ratio; MLR, monocytes-to-lymphocytes ratio.

World Health Organization. Severe cases were defined when one of the following criteria was present: (1) respiratory distress with a respiratory rate over 30 breaths per minute, (2) oxygen saturation ≤93% on room air, and (3) arterial blood oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) <300 mmHg.

Data collection

The information included demographic data, comorbidities, clinical manifestations, laboratory findings at the time of admission, days in the hospital and clinical outcomes were collected from the patient's medical and nursing records. Laboratory results included leukocytes, neutrophils, lymphocytes, monocytes, platelets, hemoglobin, C-reactive protein (CRP). NLR and MLR were calculated by dividing the absolute neutrophils and monocytes counts by the absolute lymphocyte counts.

Statistical analysis

We describe the categorical variables as number (n) and percentages (%), and continuous variables as mean±standard deviation (SD) if they are typically distributed or median with interquartile ranges (IQR) if they are not. The normal distribution test was conducted in the variables by Kolmogorov-Smirnov test. Independent group t-tests were used to compare parametric continuous variables or Mann-Whitney U tests for non-parametric continuous variables. Proportions for categorical variables were compared using the chi-square test or Fisher's exact test. Correlations between variables were assessed using Spearman's correlation analysis. Receiver operating characteristic (ROC) curves were used to study the accuracy of the various predictive tests. All statistical analyses were performed using SPSS version 25.0 software. Two-sided *P* values of less than 0.05 were considered statistically significant.

RESULTS

A total of 95 consecutive hospitalized patients with COVID-19 infection were included in this study. Among them, 55 (61,11%) were the non-severe case, and 40 (38,89%) were the severe case. The demographic and clinical characteristics of all patients were shown in Table 1.

There were many significant differences in the parameters of baseline characteristics between the severe group and the non-severe group. Patients with the severe group had older average age (57 vs. 47 years; p=0.001), more days from illness onset to admission (7 vs. 5 days; p=0.001), more comorbidities (70 vs. 52.7 %; p=0.011), and fewer survivors (42.5 vs. 100%; p<0.001) compared to patients with the non-severe group. There were no significant differences in age, gender ratio, and hospitalization days.

Table 2 presents the laboratory finding in the non-severe and severe group on admission. There were many significant differences in the parameters of laboratory findings between the non-severe group and severe group. Severe cases had higher neutrophil percentage (83,4 vs 66,3; p<0.001), higher neutrophil count (5.579 vs 3.894/L; p=0.002), higher CRP level (97 vs 11 mg/L; p<0.001), higher NLR (7.65 vs 2,92; p<0.001), higher MLR (0.46 vs 0.36; p=0.013) lower lymphocyte percentage (11 vs 24.2%; p<0.001), lower lymphocyte count (785 vs 1.401; p<0.001), lower monocyte percentage (6.4 vs 8.2%; p=0.008), and lower monocyte count (361 vs 483/L; p=0.005). There were no significant differences in leukocyte count, hemoglobin level, and platelet count between severe and non-severe groups.

Table 3 presents the results of Spearman correlation analysis between NLR and MLR with the severity of COVID-19. NLR has a significant positive correlation with disease severity (p<0.001) with moderate correlation strength (r=0.564), and MLR has a significant positive correlation with disease severity (p=0.012) with weak correlation strength (r=0.257).

Table 4 and Figure 1 presents the results of receive operating characteristics curve analysis. The area under the curve of NLR was 0.830 [95% CI (0.744 – 0.915); P<0.001] and the cut-off value of NLR as the optimal threshold for predictive the severe COVID-19 on admission is >4.84 with the sensitivity of 80%, specificity of 78.2%, the positive predictive value of 72.7%, and negative predictive value of 84.3%. The area under the curve of MLR was 0.650 [95% CI (0.538 – 0.762); P=0.013] and the best cut-off point MLR is >0.31 with the sensitivity of 85%, specificity of 47.3%, the positive predictive

Table 3. Correlation of NLR and MLR with Disease Severity

variables	r	*p*-value
Correlation NLR with disease severity	0,564	<0,001*
Correlation MLR with disease severity	0,257	0,012*

Note: NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; r, correlation coefficient; p-value derived from Spearman correlation test; Significant differences are marked by * (P<0.01).

Table 4. The cut-off value of NLR and MLR in predicting severe COVID-19

Variable	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*-value
NLR > 4.81	0.830	80	81.8	76.2	84.9	<0.001
MLR > 0.31	0.650	85	47.3	54	83.6	0.013

Note: AUC, area under the curve; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PPV, positive predictive value; NPV, negative predictive value; p-value derived from ROC analysis; Significant differences are marked by * (P < 0.01).

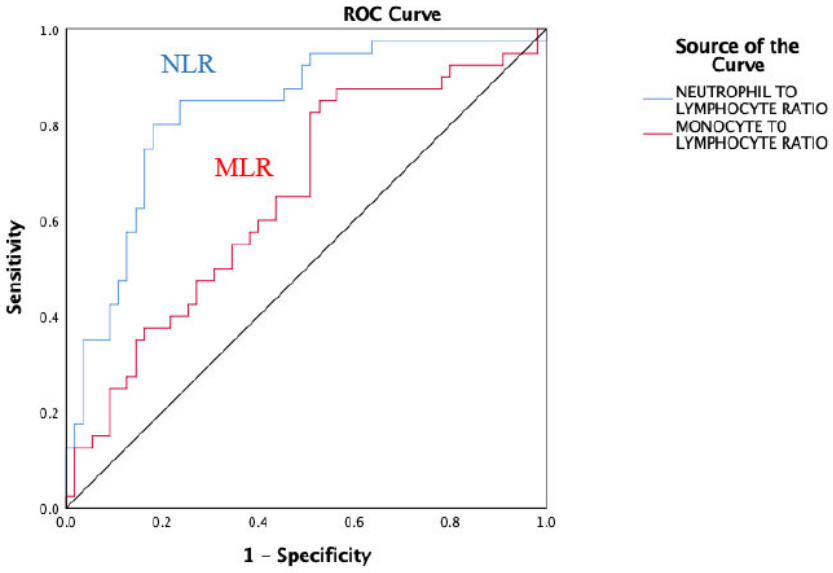

Figure 1. The ROC curves of NLR and MLR in the predicting of severe COVID-19 on admission.

value of 54%, and negative predictive value of 83.6%.

DISCUSSION

This study showed significant differences between the average age of the severe and non-severe cases (57±12 vs. 47±15 years; p=0.001). The severe cases group had a significantly higher average age than the non-severe cases group. This finding is supported by the results of a previous study conducted by Yang et al. and Ou et al.[8-10] Advanced chronological age is one of the main risk factors for the adverse outcomes of COVID-19, presumably due to immunological changes that occur during the aging process (immunosenescence and inflammaging), both characteristic of the elderly.[11]

The study also found that males who suffered severe cases were as many as 29 (72,5%) patients and 29 (52,7%) patients with non-severe cases. The number of female subjects suffering severe cases was 11 (27,5%), and patients with the non-severe case were 26 (47,3%). No significant differences were found regarding the gender of the subjects (p=0.051); this was consistent with a study obtained by Ding et al.[12] Although the differences were not statistically significant, males subject suffered from more severe cases than female subjects. These differences could be due to testosterone and estrogen differential effect on the immune system, where estrogen in females has immune-enhancing effects while testosterone has immune-suppressive effects.[13]

This study found that CRP concentration on admission was significantly higher in severe than non-severe cases. This finding is consistent with the results in the study from Qin et al. and Xie et al.[14,15] CRP is the principal downstream mediator of the acute-phase response following an inflammatory event and is primarily synthesized by IL-6-dependent hepatic biosynthesis. CRP levels are correlated with inflammation, and its concentration level is not affected by factors such as age, sex, and physical condition. Our present data indicated that the disease severity and progression were related to systemic inflammatory response severity.[16]

Neutrophile, lymphocyte and monocyte percentages in this study showed a significant difference between severe and non-severe cases. The severe cases group had a higher neutrophil percentage, lower lymphocyte percentage and lower monocyte percentage than the non-severe cases. This finding is consistent with the results in the study from Ding et al. and Qin et al.[12,14] The increased neutrophil percentage indicates the intensity of inflammatory response. The decreased lymphocyte percentage suggests the damage of the immune system. The decreased monocyte percentage indicates the antigen presentation potential of monocytes might be impaired and not effectively present the antigens to T cells. These changes make patients with severe cases lead to immune system suppression and excessive inflammatory response.[17-19]

The present study indicated a significant positive correlation between the NLR and MLR with disease severity of inpatients with COVID-19. Furthermore, there was an increase in NLR and MLR as the disease severity of inpatients with COVID-19 increases. In the severe cases, median NLR and MLR tended to be significantly higher than the non-severe cases group. This finding is consistent with the results in the study by Sun et al. and Peng et al.[4,20] In the present study, we performed the ROC analysis in order to predict the disease severity in hospitalized patients with COVID-19 and determined the cut-off levels of NLR and MLR on time to admissions. The cut-off value of NLR obtained in this study was >4.84, and MLR was >0.31 to predict severe cases. The ROC analyses performed according to the NLR cut-off values were calculated as AUC 0.83 (95% CI: 0.744 – 0.915; p<0.001) with sensitivity 80%, specificity 78.2%, negative predictive value 84.3% and positive predictive value 72.7%. The ROC analyses performed according to the MLR cut-off values were calculated as AUC 0.65 (95% CI: 0.538 – 0.762; p<0.013) with sensitivity 87.5%, specificity 43.6%, negative predictive value 82.8% and positive predictive value 53%. This finding is consistent with the results in study from Sun et al showed cut-off value of NLR was >4.5 with AUC 0.888 (95% CI: 0.812 – 0.963; p<0.001) with sensitivity 74.07%, specificity 89.89%, negative predictive value 92% and positive predictive value 69%, and cut-off value of MLR was >0.43 with AUC 0.862 (95% CI: 0.778 – 0.947; p<0.001) with sensitivity 85.19%, specificity 76.40%, negative predictive value 94.4% and positive predictive value 52.3%.[7]

The higher NLR resulted from the increased neutrophil count and decreased lymphocyte count. The NLR reflects the balance between innate immunity

(neutrophils) and adaptive immunity (lymphocytes). In severe cases, the higher NLR indicated that the immune system in severe cases was dysregulated more severely and could not dampen the overactive innate immune response. These inflammatory overactivation responses might aggravate the production of a cytokine storm and worsen damaged tissue.[21,22]

The rise of MLR in this study results from decreased lymphocyte percentage. The MLR reflects the immune capacity to mount an effective immune response against infection. The higher MLR in severe cases indicated that the immune system in severe cases was damaged more severely and unable to make a normal immune response to infection. This low immune response state represents an indication of severe immunosuppressive conditions that lead to immune paralysis with increased susceptibility to hospital-acquired infections.[7,23]

Our results also showed significant differences between the clinical outcomes of severe and non-severe cases groups. That 24,21% of this study was non-severe, and all of these cases were approximately 57,5% of severe cases. These results indicate significant differences between the clinical outcomes of severe and non-severe cases groups. The majority of the non-survivor case had comorbidities and aged older than 50 years, which is consistent with the report by Guisado-Vasco et al.[24]

There were several limitations to our study that might cause some potential bias. First, it was a retrospective study, and the sample is small. Second, the data were obtained from a single clinical research center. Therefore, an additional large-scale multicenter study will be required to confirm our findings further.

CONCLUSION

NLR and MLR at admission had a significant positive correlation with the disease severity. The sensitivity of NLR is higher than MLR for predicting severe cases in hospitalized patients with COVID-19 infection. Therefore, patients with high NLR and MLR on admission need more intensive attention in clinical practice.

DISCLOSURE

Ethical Clearance

This study has received ethical approval from the Research Ethics Committee of Universitas Sumatra Utara, Medan, Indonesia.

Conflict Of Interest

The authors declare that there is no competing interest regarding the manuscript.

Funding

The authors are responsible for study funding of the study without any grant, scholarship, sponsorship, or other funding resources.

Author's Contribution

All of the authors equally contributed to the study from the conceptual framework, data gathering, data analysis until reporting the results through publication.

REFERENCES

1. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses*. 2020; 12 (4): 372; doi: 10.3390/v12040372.
2. World Health Organization. Clinical management of COVID-19: interim guidance, May 27 2020. World Health Organization. https://apps.who.int/iris/handle/10665/332196.
3. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. *J Infect Public Health*. 2020; 13(5): 667-673.
4. Sun Q, Qiu H, Huang M, Yi Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care*. 2020;10 (1): 33. doi: 10.1186/s13613-020-00650-2
5. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, Jager CPC, Loonen AJM, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. *J Infect*. 2019; 78 (5): 339-348
6. Huang Y, Liu A, Liang L, Jiang J, Luo H, Deng W, et al. Diagnostic value of blood parameters for community-acquired pneumonia. *Int Immunopharmacol*. 2018; 64:10-15.
7. 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; 507:174-180.
8. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. *Int J Infect Dis*. 2020; 95: 332-339.
9. 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.
10. Ou M, Zhu J, Ji P, Li H, Zhong Z, Li B et al. Risk factors of severe cases with COVID-19: a meta-analysis. *Epidemiol Infect*. 2020; 148(175):1–11.
11. Domingues R, Lippi A, Setz C, Outeiro TF, Krisko A. SARS-CoV-2, immunosenescence and inflammaging: partners in the COVID-19 crime. *Aging*. 2020; 12(18): 18778-18789.
12. Ding X, Yu Y, Lu B, Huo J, Chen M, Kang Y et al. Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019. *Clin Chem Lab Med*. 2020; 58(8): 1365-1371.
13. Pradhan A, Olsson P. Sex differences in severity and mortality from COVID-19: are males more vulnerable?. *Biol Sex Differ*. 2020; 11: 53
14. Qin C, Zhou L, Hu Z, Yang S, Tao Y, Xie C, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis*. 2020; 234-239.
15. Xie L, Wu Q, Lin Q, Liu X, Lin W, Hae S, et al. Dysfunction of adaptive immunity is related to severity of COVID-19: a retrospective study. *Ther Adv Respir Dis*. 2020; 14:1-15.
16. Wang D, Li R, Wang J, Jiang Q, Gao C, Yang J et al. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. *BMC Infect Dis*. 2020; 20(1): 519-528.
17. Newton AH, Cardani A, Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. *Semin Immunopathol*. 2016; 38:471-482.
18. Hajghorbani T, Zafari P, Masoumi T, Rajabinejad M, Jafari SR. The role of dysregulated immune responses in COVID-19 pathogenesis. *Virus Res*. 2020; 290: doi: 198197. 10.1016/j.virusres.2020.198197
19. Garcia LF. Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol*. 2020; 11: 144-68.

20. Peng J, Qi D, Yuan G, Deng X, Mei Y, Feng L et al. Diagnostic value of peripheral hematologic markers for coronavirus disease 2019 (COVID-19): a multicenter, cross-sectional study. *J Clin Lab Anal*. 2020; 34 (10): e23475. doi: 10.1002/jcla.23475.
21. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: Current state of the science. *Immunity*. 2020;52(6):910-941.
22. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammation marker with the severity of COVID-19: a meta-analysis. *Int J Infect Dis*. 2020; 96:467-474.
23. Praveen T, Desai D, Soneja M, Wig N. Immune dysregulation in COVID-19 and its therapeutic implication. *J Clin Sci Res*. 2020; 9: 37-41.
24. Vasco GP, Ortega AR, Carralo MM, Gonzales C, Santacruz AR, Cortijo LG, Fernandez G. Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: a retrospective observational study (COQUIMA cohort). *EClinicalMedicine*. 2020: 100591.