

## THE GENDER DIFFERENCE AND CORRELATIONS OF NEUTROPHIL-TO-LYMPHOCYTE RATIO AND D-DIMER AMONG HOSPITALIZED PATIENTS WITH COVID-19 IN NORTH MACEDONIA

*B. Ilkovska<sup>1</sup>, B. Kotevska Trifunova<sup>2</sup>, P. Avramovski<sup>3</sup>*

<sup>1</sup>PHO Clinical Hospital Dr. Trifun Panovski, Department of Laboratory Medicine – Bitola, North Macedonia

<sup>2</sup>Adzibadem Citi Clinic UMHAT Tokuda, Department of Dermatovenerology – Sofia, Bulgaria

<sup>3</sup>PHO Clinical Hospital Dr. Trifun Panovski, Department of Internal Medicine – Bitola, North Macedonia

## РАЗЛИКАТА ПО ПОЛ И КОРЕЛАЦИИТЕ НА СЪОТНОШЕНИЕТО НЕУТРОФИЛИ КЪМ ЛИМФОЦИТИ И D-ДИМЕР СРЕД ХОСПИТАЛИЗИРАНИТЕ ПАЦИЕНТИ С COVID-19 В СЕВЕРНА МАКЕДОНИЯ

*Б. Илковска<sup>1</sup>, Б. Котевска Трифунова<sup>2</sup>, П. Аврамовски<sup>3</sup>*

<sup>1</sup>Отделение „Лабораторна медицина“, ОЗИ Клинична болница „Д-р Трифун Пановски“ – Битоля, Северна Македония

<sup>2</sup>Отделение „Дерматовенерология“, Аджибадем Сити Клиник, УМБАЛ „Токуда“ – София, България

<sup>3</sup>Отделение „Вътрешна медицина“, ОЗИ Клинична болница „Д-р Трифун Пановски“ – Битоля, Северна Македония

**Abstract. Introduction:** Coronavirus disease has had a catastrophic effect on the world's demographics, resulting in more than 5.8 million deaths worldwide and more than 422 million confirmed cases reported globally. The aim of this study was to assess the utility of the neutrophil-lymphocyte ratio (NLR), a simple, widely available, and inexpensive laboratory examination, as a reliable inflammatory biomarker for COVID-19 patients. By comparing the NLR with the D-dimer plasma level, we also want to analyze gender differences between hematological and hemostatic parameters in patients with COVID-19. **Methods:** This study was carried in 2021 in Public Health Organization Clinical Hospital “Dr. Trifun Panovski” in Bitola in 2021. Our study describes the laboratory characteristics of 40 COVID-19 patients hospitalized in the Department of Infective Diseases. **Results:** The overall mean count of white blood cells count was  $9 \pm 0.28 \times 10^9$ . The overall mean of NLR was  $9.3 \pm 5.6$ . The overall mean of CRP and D-dimer was  $58.7 \pm 41.22$  mg/l and  $5624 \pm 1944$  FEU ng/ml, respectively. NLR, CRP and D-dimer in the male and female groups in patients with COVID-19 did not show statistically significant differences. We confirmed a significant correlation between NLR and D-dimer levels in patients with COVID-19. **Conclusion:** NLR was found to correlate well with the established inflammatory marker CRP and coagulation marker D-Dimer, which is capable of predicting severe COVID-19. Therefore, NLR that is easily calculated at the emergency department using routine laboratory tests, even in a remote area, may serve as a practical and cost-effective marker for guiding the physician in awareness regarding the need for intensive care.

**Key words:** neutrophil-lymphocyte ratio, NLR, D-dimer, COVID-19

**Резюме. Въведение:** Коронавирусната болест има катастрофален ефект върху демографията в света, което води до повече от 5,8 млн. смъртни случая по света и повече от 422 млн. потвърдени случая, докладвани в световен мащаб. **Целта** на това проучване беше да се оцени полезността на съотношението неутрофили-лимфоцити (NLR) – просто, широко достъпно и евтино лабораторно изследване, като надежден възпалителен биомаркер за пациенти с COVID-19. Чрез сравняване на NLR с плазменото ниво на D-димер, ние също така анализирахме различията между хематологичните и хемостатичните параметри според пола при пациенти с COVID-19. **Материал и методи:** Проучването бе проведено през 2021 г. в Клинична болница „Д-р Трифун Пановски“ в град Битоля (Северна Македония). Нашето проучване описва лабораторните характеристики на 40 пациенти с COVID-19, хоспитализирани в Отделението по инфекциозни болести. **Резултати:** Общият среден брой бели кръвни клетки е  $9 \pm 0,28 \times 10^9$ . Общата средна стойност на NLR е  $9,3 \pm 5,6$ . Общата

средна стойност на CRP и D-димера е съответно  $58,7 \pm 41,22$  mg/l и  $5624 \pm 1944$  FEU ng/ml. NLR, CRP и D-димер при мъжките и женските групи пациенти с COVID-19 не показват статистически значими разлики. Ние потвърдихме значителна корелация между нивата на NLR и D-димера при пациенти с COVID-19. **Заклучение:** Установено е, че NLR корелира добре с установения възпалителен маркер CRP и коагулационен маркер D-димер, който е в състояние да предскаже тежък COVID-19. Следователно NLR, който лесно се изчислява в спешното отделение с помощта на рутинни лабораторни тестове, дори в отдалечен район, може да служи като практичен и рентабилен маркер за насочване на лекаря към осъзнаването на необходимостта от интензивно лечение.

**Ключови думи:** съотношение неутрофили-лимфоцити, D-димер, COVID-19

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), the highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a catastrophic effect on the world's demographics [1], resulting in more than 5.8 million deaths worldwide and more than 422 million confirmed cases reported globally. In the Republic of North Macedonia, according to the latest statistics until March 2022, 301,583 Coronavirus cases were confirmed, and 9150 patients ended in lethal outcomes. All people are susceptible to the development of SARS-CoV-2-related disease, but the course of the disease is different in each patient, as is the clinical manifestation of the disease, which may be asymptomatic but may present with a more pronounced variable clinical manifestations such as fever, dry cough, fatigue and myalgia, and especially seriously ill patients, in particular certain specific populations, presented with dyspnea and hypoxemia, which may result in acute respiratory distress syndrome. In addition to severe respiratory damage, the cardiovascular, digestive, urinary and immune systems are also greatly affected, affecting the prognosis [2]. Several abnormal hematological parameters were reported in COVID-19 patients [3-6], including lymphopenia, neutrophilia, and elevated levels of D-dimer and fibrinogen, but the clinical implication of these indexes remains elusive.

Coagulation dysfunction has been found in a high proportion of COVID-19 cases, as evidenced by increasing D-dimer levels, prolonged prothrombin time, and overt thrombotic manifestations [7]. Clinical reports demonstrated that patients infected with SARS-CoV-2 often present with thrombocytopenia and increased D-dimer, and patients with severe infection exhibit an increased risk of disseminated intravascular coagulation (DIC) [5]. DIC, a secondary syndrome of intravascular coagulation due to local damage caused by different etiologies, is a manifestation of coagulation failure and an intermediate link in the development of multiorgan failure [8]. Abnormal coagulation in patients with COVID-19 is characterized by elevated fibrinogen and D-dimer

in parallel with increased inflammatory markers [5]. At the same time, prothrombin time and partial thrombin activation time were prolonged while platelets were reduced. This suggests that an excessive inflammatory response may activate the clotting pathway, leading to increased consumption of coagulation factors and platelets. During inflammation of the systemic organs, damage to the microvascular system occurs, and thus the coagulation system is activated and manifests itself with systemic microangiitis and extensive microthrombosis, which eventually leads to systemic dysfunction of several organs [2]. The neutrophil-lymphocyte ratio (NLR) is a parameter that we have recently used to assess the inflammatory status of the subject. NLR can be easily calculated from a complete blood count, which is the most commonly used laboratory practice test.

Whether measured in isolation or in combination with other risk factors, NLR has been identified as a good predictive value for distinguishing severe cases from mild/moderate cases and is associated with COVID-19 mortality [9-13]. On the other hand, the NLR ratio is an easy and rapid prognostic marker in a myriad of clinical conditions that include solid tumors [14], chronic obstructive pulmonary disease [15], liver cirrhosis [16], rheumatoid arthritis [17], acute pancreatitis [18], sepsis [19] and psoriasis [20].

However, our knowledge of the value of NLR in predicting the clinical condition of the disease (e.g., mild/moderate progression to severe/critical, severe to critical deterioration) and severe clinical outcomes (e.g., shock, death) are scarce.

Laboratory monitoring of specific parameters such as D-dimer, fibrinogen, platelet count and prothrombin time is invaluable and crucial for all hospitalized and severe cases of COVID-19.

In this study, we would like to assess the utility of NLR, a simple, widely available, and inexpensive laboratory examination, as a reliable inflammatory biomarker for COVID-19 patients in North Macedonia. By comparing NLR level with D-dimer plasma level, we also want to analyze gender differences between hematological and hemostatic parameters in patients with COVID-19.

## MATERIALS AND METHODS

This study was carried out at the Department of Medical Biochemistry and Department of infective diseases of Public Health Organization Clinical Hospital "Dr. Trifun Panovski" in Bitola from January to November 2021. Our study describes the laboratory characteristics of 40 COVID-19 patients hospitalized in the Department of infectious diseases with a moderate stage of the disease from 30 to 87 years old.

The Ethics Committee of Health Organization Clinical hospital "Dr. Trifun Panovski" approved the study, and all the procedures were performed in accordance with ethical approval institutional guidelines. The protocol for this study was guided by the ethical norms of the latest Declaration of Helsinki. First, we obtained written consent from participants to participate in this study.

### Clinical and laboratory measurements

Patient respiratory samples, including nasopharyngeal swabs, were collected, and real-time polymerase chain reaction (RT-PCR) was used to confirm COVID-19 infection. Data include medical history, a physical examination, questionnaire information and laboratory findings of each patient. A confirmed case was defined by a positive result of RT-PCR performed in nasopharyngeal swab specimens.

Blood samples were collected after 12 hours of fasting. Complete blood count (CBC): CBC was determined in potassium ethylenediaminetetraacetic acid (K-EDTA) blood samples using Sysmex XP 300/ Sysmex XS 1000 (Sysmex Co, Kobe, Japan) according to the manufacturer's instructions. The obtained indicators were as follows: white blood cell count (WBC x 10<sup>9</sup>/L), neutrophil count (NEUT x

10<sup>9</sup>/L), lymphocyte count (LYMPH x 10<sup>9</sup>/L)), hemoglobin (HGB, g/l), platelet (PLT x 10<sup>9</sup>/L).

Biochemical analyzes were performed on an automated integrated analyzer Abbot Architect CI 4100 following the analyzer manufacturer's instructions. We determined hypersensitive C-reactive protein (hsCRP) and iron.

We determined plasma levels of D-dimer by IMMULITE® 2000 XPi device (Diagnostic Products Corporation, Los Angeles, CA, USA), which runs with the chemiluminescence method and belongs to BIO-DPC Company.

Data analysis was supported by the Statistical Package for the Social Science (SPSS) version 22. The continuous variables were denoted as mean ± standard deviation. The normality test was performed using the Shapiro-Wilk test. An odd t-test or Mann-Whitney test was used to compare the mean NLR and D-dimer values between men and women in the COVID-19 group. We used a Pearson or Spearman test to determine the correlation between the NLR and the D-dimer.

## RESULTS

We recruited 40 COVID-19 patients during the study period; half were male. The mean age of patients was 70 ± 30.4 years.

The overall mean white blood cell count was 9 ± 0.28 x 10<sup>9</sup>. The overall mean value of NLR was 9.3 ± 5.6. The overall mean levels of CRP and D-dimer were 58.7 ± 41.22 mg/l and 5624 ± 1944 FEU ng/ml, respectively. Details regarding our subject's characteristics and the comparison between males and females in the COVID-19 group can be seen in Table 1.

Table 1. Characteristics of all hospitalized patients with COVID-19.

Characteristics	All (n = 40)	Males (n = 20)	Females (n = 20)	P-value
Age, mean ± SD	70,1 ± 30.4	70 ± 6.3	70 ± 2.82	1
Gender (males/females)	40	20	20	
Hemoglobin, mean ± SD (g/l)	132.3 ± 39.6	142 ± 10.6	122 ± 8.48	< 0.0001
White Blood Cell count mean ± SD (10 <sup>9</sup> /L)	9.1 ± 0.3	10 ± 1.13	8 ± 2.26	0.0011
Neutrophil count mean ± SD (10 <sup>9</sup> /L)	7.28 ± 1.41	8 ± 2.82	6 ± 1.16	0.0057
Lymphocyte count mean ± SD (10 <sup>9</sup> /L)	1.39 ± 1.13	1 ± 1.2	2 ± 0.56	0.0017
Platelet, mean ± SD	266.3 ± 155.6	274 ± 38.8	259 ± 84.14	0.4735
CRP, mean ± SD (mg/l)	58.69 ± 41.22	69 ± 153	49 ± 25.95	0.5678
NLR, mean ± SD	9.27 ± 5.66	12 ± 8.7	6 ± 4.8	0.0103
D-dimer, mean ± SD (FEU ng/ml)	5624 ± 1944	5829 ± 630	5421 ± 1634	0.3040

The results are presented as mean values ± standard deviation.

In our study, the Mann-Whitney test showed that NLR values in males and females in the group of patients with COVID did not show a statistically significant difference since the p-value was 0.35758. A similar finding was also found by comparing the NLR with CRP ( $p = 0.35758$ ) and D-dimer ( $p = 0.38974$ ).

Fig. 1 presents the significant correlation between NLR and D-dimer. The T-Test calculator for two independent means confirmed a significant correlation between NLR and D-dimer levels ( $p < 0.00001$ ) with a t-value of -13.86583.

Mann-Whitney U test calculator showed a significant correlation between NLR and D-dimer level. The z-score was -8.90445, and  $p \leq 0.00001$ .

Hemocytopenia was common, including lymphopenia and thrombocytopenia (90% and 15%, respectively). The incidence of anemia was 22% of all included patients.

Overall, males and females had a similar median age of 70 years. We observed statistically significant differences in hemoglobin, white blood cell count, neutrophil count, lymphocyte count, and NLR values between the female and male groups. Females and males had comparable levels of D-dimer and CRP, but males had lower absolute lymphocyte counts, higher NLR, and higher platelet and neutrophil counts than females

## DISCUSSION

The aim of our study was to determine whether there is an association between NLR and D-dimer. As can be seen, we found an association between NLR, which is a marker of systemic inflammation, and D-dimer, which is a marker of impaired hemo-

stasis, which includes hypercoagulation and thrombosis. The NLR's role as a prognostic marker for COVID-19 patients was extensively studied. NLR may become a reliable, accessible, and cost-effective inflammation parameter, especially in developing countries such as North Macedonia during the COVID-19 pandemic. Recently, NLR was found to have greater predictive power than traditional inflammatory markers, such as CRP, white blood cell count and neutrophil count, in community-acquired pneumonia [21, 22]. Jin YH et al. discovered that at the early stage of COVID-19, the total number of leukocytes in peripheral blood is normal or decreases, while the lymphocyte count decreases [23].

Our research found statistically significant differences in hemoglobin, white blood cell count, neutrophil count, lymphocyte count, and NLR values between the female and male groups. Females and males had comparable levels of D-dimer and CRP, but males had higher absolute lymphocyte counts, higher NLR, and higher platelet and neutrophil counts than females. Males have higher values of hemoglobin compared to females. With laboratory measurements in the first 48 hours of admission, Scully EP et al. discovered that females and males had comparable levels of D-dimer and erythrocyte sedimentation rate, but males had lower absolute lymphocyte counts, higher NLR and higher ferritin, IL-6 and CRP levels than females. Age-stratified analyses demonstrated differential effects of age; with increasing age, there was less difference between the median values of males and females for CRP, ferritin, and IL-6 [24]. A study by Simadibrata et al., including more than 5000 COVID-19 patients, found that higher NLR levels on admission were as-

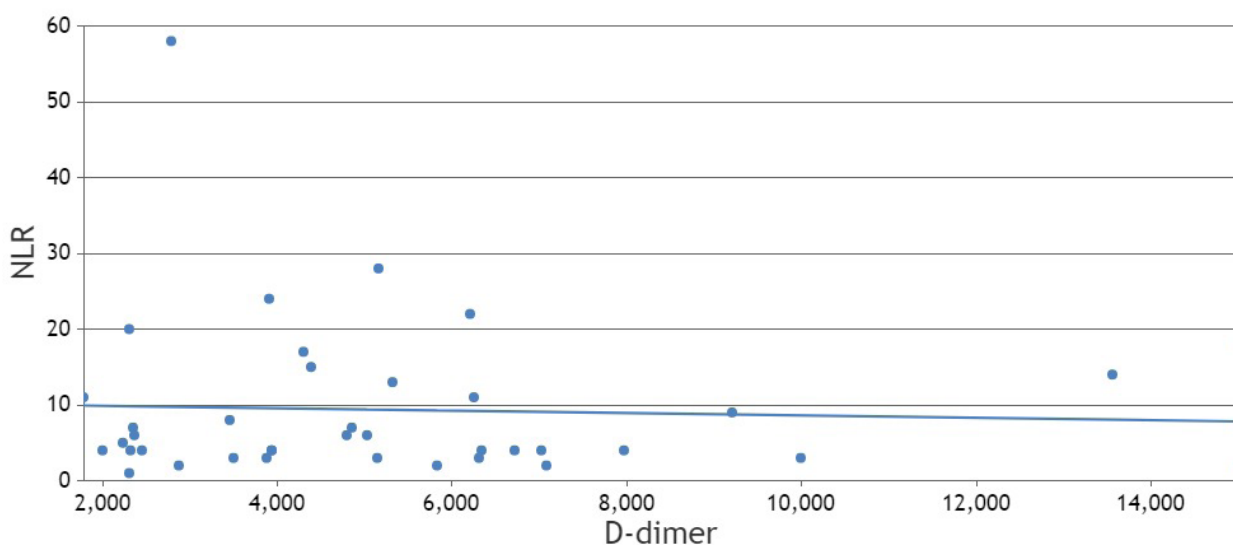


Fig. 1. Correlation between NLR and D-dimer levels in patients with COVID-19

sociated with 2.7 times higher mortality risk than patients with normal NLR. The higher NLR level was also associated with a more severe COVID-19 disease course [25].

The elevation of NLR value may be explained by the increased level of neutrophils due to inflammation response and lymphocytopenia. Lymphocytopenia occurred in 90% of severe COVID-19 cases. A systematic review by Zhao et al. concluded that COVID-19 patients with lymphocytopenia are associated with nearly three times increased risk for severe disease. Lymphocytopenia in patients with COVID-19, such as SARS-CoV-2, is thought to be the result of lymphocyte apoptosis and pyroptosis, suppression of bone marrow due to the release of proinflammatory cytokines released, thymus suppression, activation-induced cell death of lymphocytes, tissue redistribution of lymphocytes, and several other pathways [26]. Another research by Rostami et al. also found that an increase in D-dimer level was linked to poor prognosis, and they recommended measuring D-dimer level in all COVID-19 patients [27].

In our research, we found significantly higher D-dimer levels in the severe COVID-19 patients' group. Isbaniah et al. found that NLR and D-dimer value on admission was important for predicting the clinical outcome of Indonesian COVID-19 patients [28]. Man et al. found that NLR was significantly correlated with D-dimer in predicting COVID-19 severity ( $p < 0.001$  and  $r = 0.49$ ) [29]. The dynamic change of NLR and D-dimer level can discriminate severe COVID-19 cases from mild/moderate ones in the days after admission.

The limitation of our study is related to the small number of subjects; therefore, further study with a larger sample size is warranted to establish a possible stronger correlation between NLR and D-dimer level among North Macedonian COVID-19 patients. The ideal marker to help us assess the severity of the disease in patients with COVID-19 should be readily available, inexpensive and accurate. We believe that exposing patients to a higher cost of doing a huge range of laboratory tests has a significant impact on the financial situation, and we as doctors need to be careful about that. In summary, our results also indicated that the epidemiological and clinical features of COVID-19 cases in North Macedonia are similar to previous reports.

## CONCLUSION

The neutrophil-to-lymphocyte ratio has been found to correlate with markers of inflammation and coagulation and has the power to help prediction of

severity of a COVID-19 infection. Therefore, NLR that is easily calculated at the emergency department using routine laboratory tests even in a remote area may serve as a practical and cost-effective marker for guiding the physician in awareness regarding the need for intensive care.

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Conflict of interest: None declared.

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## References

1. Cascella M, Rajnik M, Aleem A et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls, 2022.
2. Zhao W, Li H, Li J et al. The mechanism of multiple organ dysfunction syndrome in patients with COVID-19. *J Med Virol*, 2022.
3. Guan W, Ni Z, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. *New Engl J Med*, 2020;382(18):1708-1720.
4. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 2020;395(10223):497-506.
5. Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, 2020;395(10223):507-513.
6. Fan BE, Chong V, Chan S et al. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol*, 2020;95(11):1442.
7. Lopes-Pacheco M, Silva PL, Cruz FF et al. Pathogenesis of Multiple Organ Injury in COVID-19 and Potential. *Therapeutic Strategies*. *Front Physiol*, 2021;28(12):593223.
8. Arachchilage DRJ, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*, 2020;18(5):1233-1234.
9. Fu J, Kong J, Wang W et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. *Thromb Res*, 2020;192:3-8.
10. Wang CZ, Deng RR, Gou LY et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. *Ann Transl Med*, 2020;8(9):593.
11. Shang WF, Dong JW, Ren YL et al. The value of clinical parameters in predicting the severity of COVID-19. *J Med Virol*, 2020;92(10):2188-92.
12. Yang AP, Liu JP, Tan WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Int Immunopharmacol*, 2020;84:106504.
13. Liu YW, Du XB, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Inf Secur*, 2020;81:e6-e12.
14. Templeton AJ, McNamara MG, Šeruga B et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*, 2014, 106:dju124.
15. Perrotta F, Nigro E, Pafundi PC et al. Adiponectin is associated with neutrophils to lymphocyte ratio in patients with chronic obstructive pulmonary disease. *COPD*, 2020;18:70-5.
16. Peng Y, Li Y, He Y, Wei Q et al. The role of neutrophil to lymphocyte ratio for the assessment of liver fibrosis and cirrhosis: a systematic review. *Expert Rev Gastroenterol Hepatol*, 2018;12:503-13.
17. Erre GL, Paliogiannis P, Castagna F et al. Meta-analysis of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in rheumatoid arthritis. *Eur J Clin Invest*, 2019;49:e13037.

18. Kong W, He Y, Bao H et al. Diagnostic value of neutrophil-lymphocyte ratio for predicting the severity of acute pancreatitis: a meta-analysis. *Dis Markers*, 2020;9731854.
19. Huang Z, Fu Z, Huang W et al. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med*, 2020;38:641-7.
20. Paliogiannis P, Satta R, Deligia G et al. Associations between the neutrophil-to-lymphocyte and the platelet-to-lymphocyte ratios and the presence and severity of psoriasis: a systematic review and meta-analysis. *Clin Exp Med*, 2019; 19:37-45.
21. De Jager CP, Wever PC, Gemen EF et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One*, 2012;7(10):e46561.
22. Cataudella E, Giraffa CM, Di Marca S et al. Neutrophil-to-lymphocyte ratio: an emerging marker predicting prognosis in elderly adults with community-acquired pneumonia. *J Am Geriatr Soc*, 2017;65(8):1796-801.
23. Jin YH, Cai L, Cheng ZS et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*, 2020;7(1):4.
24. Scully EP, Schumock G, Fu M et al. JH-CROWN registry team. Sex and gender differences in COVID testing, hospital admission, presentation, and drivers of severe outcomes in the DC/Maryland region. *medRxiv*, 2021; 31;8(9):ofab448.
25. Simadibrata DM, Calvin J, Wijaya AD et al. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. *Am J Emerg Med*, 2021;42:60-9.
26. Zhao Q, Meng M, Kumar R et al. Lymphopenia is associated with severe Coronavirus disease 2019 (COVID-19) infections: A systematic review and meta-analysis. *Int J Infect Dis*, 2020;96:131-5.
27. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: A systematic review. *Expert Rev Hematol*, 2020;13(11):1265-75.
28. Isbaniah F, Juliani T, Damayanti T et al. The role neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and D-dimer in predicting the outcome of confirmed COVID-19 patients. *J Respir Indones*, 2021;41(4):236-44.
29. Man MA, Rajnoveanu RM, Motoc NS et al. Neutrophil-to-lymphocyte ratio, platelets-to-lymphocyte ratio, and eosinophils correlation with high-resolution computer tomography severity score in COVID-19 patients. *PLoS One*, 2021;16(6):e0252599.

✉ *Address for correspondence:*  
 Biljana Ilkovska, MD, PhD  
 29 Dimce Lahcanski Str  
 7000 Bitola  
 North Macedonia  
 Tel.: +38971361262  
 e-mail: drbiljanailkovska@yahoo.com