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NEUTROPHIL TO LYMPHOCYTE RATIO AND C-REACTIVE PROTEIN LEVEL IN SEVERE VERSUS NON-SEVERE COVID-19 PATIENTS IN NORTH MACEDONIA

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СЪОТНОШЕНИЕТО НА НЕУТРОФИЛИ И ЛИМФОЦИТИ И НИВОТО НА С-РЕАКТИВЕН ПРОТЕИН ПРИ ТЕЖКИ СПРЯМО НЕТЕЖКИ ПАЦИЕНТИ С COVID-19 В СЕВЕРНА МАКЕДОНИЯ

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Abstract. Background. 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. **Aims:** This study aimed to investigate NLR and CRP to identify potential clinical predictors and analyze differences among the severe and non-severe COVID-19 patients. Laboratory monitoring of certain parameters such as CRP, leukocyte and platelet count is invaluable and crucial for all cases of COVID-19. **Study Design:** A single-center retrospective study was conducted on the recruited patients who were referred to Clinical Hospital, Bitola, North Macedonia, from January to April, 2022. **Material and Methods:** Serum CRP level as well as plasma D-dimer level were measured according to standard methods using Abbott Alinity Ci analyzer. Complete blood counts (white blood cell, neutrophil, lymphocyte and platelet counts) were measured in EDTA-anticoagulated blood samples using Sysmex XS1000i analyzer (Sysmex). Afterwards, the NLR value was calculated for each of the patients. **Results:** Data of 200 patients (94 female, 106 male) were evaluated. The mean age was 66.63 ± 49.49 years in the group with severe patients and 51.45 ± 19.01 years in the group of non-severe patients. Compared with the patients with a non-severe COVID-19 infection, the severe COVID-19 patients had higher levels of CRP, D-dimer, NLR, platelets, neutrophil count and lower levels of lymphocyte and hemoglobin. In the correlation analysis of NLR and CLR indices as inflammatory biomarkers in the COVID-19 patients, a positive correlation was observed between NLR values and CRP in the severe vs non-severe COVID-19. Also, NLR significantly correlated with D-dimer, hemoglobin and platelets in the severe vs non-severe COVID-19 patients.

Key words: COVID-19, CRP, NLR, neutrophil

Резюме. Въведение. Инфекцията с коронавирусната болест 2019 (COVID-19) се превърна в значим здравен проблем за световната общност от началото на 2020 г. Заболяването е силно инфекциозно и има широк диапазон на клиничните прояви. **Цел:** Целта на изследването е да се анализират NLR и CRP, за да се установят потенциалните клинични предиктори и да се определят разликите между тежките и нетежките пациенти с COVID-19. Лабораторният мониторинг на специфични параметри като CRP и нивото на левкоцитите и тромбоцитите играе неоценима и решаваща роля при всички случаи на COVID-19. **Дизайн на изследването:** Проведе се едноцентрово ретроспективно проучване на рекрутирани пациенти, които са насочени към Клинична болница, Битоля, Северна Македония, от януари до април 2022 г. **Материал и методи:** Серумните нива на CRP и плазменото ниво на D-димер бяха измерени по стандартни методи с апарат Abbott Alinity Ci. Извърши се изслед-

ване на пълната кръвна картина (брой на левкоцитите, неутрофилите, лимфоцитите и тромбоцитите) в кръвни проби, антикоагулирани с EDTA, чрез апарат Sysmex XS1000i (Sysmex). След това се изчисли стойността на NLR за всеки пациент. **Резултати:** Извърши се анализ на данните на 200 пациенти (94 жени, 106 мъже). Средната възраст в групата с тежки пациенти беше $66,63 \pm 49,49$ г. и $51,45 \pm 19,01$ г. в групата с нетежки пациенти. При сравнението с пациентите с нетежка COVID-19 инфекция се установи, че тежките COVID-19 пациенти имат по-високи нива на CRP, D-димер, NLR и брой на тромбоцитите и неутрофилите, както и по-ниски нива на лимфоцитите и хемоглобина. При корелационния анализ на индексите NLR и CLR като възпалителни биомаркери при COVID-19 пациенти се установи положителна корелация между стойностите на NLR и CRP при тежък спрямо нетежък COVID-19. Освен това, NLR корелира значимо с D-димера, хемоглобина и тромбоцитите при тежки спрямо нетежки COVID-19 пациенти.

Ключови думи: COVID-19, CRP, NLR, неутрофили

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 [1]. COVID-19 patients are classified according to clinical presentation of disease as mild, moderate, severe and critical. The main criteria for classification of patients are involvement of lung and severity of pneumonia [2]. Although 81% of the cases have a mild course, a severe course is observed in 14% of cases and a critically severe course is observed in 5% [3]. Prognosis is poor and mortality is high in critically severe cases [4]. Fever, cough, dyspnea, fatigue, and myalgia are among the clinical symptoms, and the ground-glass appearance on computed tomography is accepted as the typical finding [5]. Its pathogenesis includes the inflammatory process associated with vasculitis, the complement cascade and pro-inflammatory cytokines, and the process results in serious organ damage, particularly lung and cardiovascular damages [6].

C-reactive protein (CRP) is a widely used diagnostic marker primarily used to assess ongoing inflammation. It appears in blood within 6-10 hours of a tissue-damaging event and decreases exponentially over 18-20 h [7]. The complete blood count is the most available, efficient, and economic examination. Moreover, peripheral white blood cell (WBC) count and neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR) are indicators of the systematic inflammatory response [8]. Recent studies have shown that inflammatory markers like C-reactive protein (CRP), and immune-cell-based inflammatory indices such as neutrophil to lymphocyte ratio (NLR), were significantly associated with adverse disease outcomes of COVID-19 and have been considered useful indica-

tors for diagnosis and prognosis of various infectious diseases, including COVID-19 infection [9].

Several previous studies have been performed on neutrophils, lymphocytes, and CRP in COVID-19 patients [10, 11], but little is known about their association with disease severity in North Macedonia. This study aimed to investigate NLR and CRP to identify potential clinical predictors and analyze differences among severe and non-severe COVID-19 patients. Laboratory monitoring of certain parameters such as CRP, leukocyte and platelet count is invaluable and crucial for all cases of COVID-19.

MATERIAL AND METHODS

Participants

A single-center retrospective study was conducted on recruited patients, who were referred to Clinical Hospital, Bitola, North Macedonia, from January to April, 2022. Positive COVID-19 patients were classified into two groups based on their clinical reports (non-severe and severe). According to clinical symptoms, CT findings, and laboratory results we classified patients as follows: 100 patients were listed as non-severe and 100 had developed into severe infection. Data for each patient, such as age and gender, was collected from medical records. Blood samples were collected for laboratory assessments, including complete blood counts with differential count and CRP levels. All COVID-19 cases had positive PCR test results in collected nasopharyngeal swab samples to detect SARS-CoV-2. Serum CRP level as well as plasma D-dimer level were measured according to standard methods using Abbott Alinity Ci analyzer. Complete blood counts (white blood cell, neutrophil, lymphocyte and platelet counts) were measured in EDTA-anticoagulated blood samples using Sysmex

XS-1000i analyzer (Sysmex). Afterwards, NLR values were calculated for each of the patients.

Statistical Analysis

IBM 22.0 version was used for statistical analysis. The Mann-Whitney U-test was used for non-parametric analysis. Descriptive analyses were presented as a mean and standard deviation. The chi-square and Fisher's exact test were employed for categorical analyses. Variables were compared using Student's t test. $P < 0.05$ was considered significant.

RESULTS

Data of 200 patients (94 female, 106 male) were evaluated. The mean age was 66.63 ± 49.49 years in the group with severe patients and 51.45 ± 19.01 years in the group of non-severe patients. Among them, 29% were in the age range of 15 to 49 years, 28% were in the age range of 50 to 64 years and 43% were older than 65 years. The common laboratory indicators such as lymphocyte, neutrophil, WBC, CRP and D-dimer were achieved from the enrolled 200 patients and compared between the severe and non-severe patients.

Table 1. Demographic and laboratory characteristics of severe and non-severe COVID-19 patients

Variables	Severe (n = 100)	Non-severe (n = 100)	P
Gender:			
Males	57	49	
Females	43	51	
Age, mean \pm SD	66.63 ± 49.49	51.45 ± 19.01	0.0046
15-49 y	13	46	
50-64 y	22	35	
≥ 65 y	65	19	
White Blood Cell count, mean \pm SD ($10^9/L$)	10.45 ± 1.06	6.24 ± 0.42	< 0.0001
Hemoglobin, mean \pm SD (g/l)	135.77 ± 41.01	146.12 ± 13.43	0.0174
Platelet, mean \pm SD	312.67 ± 65.76	243.13 ± 167.58	0.0002
Neutrophil count mean \pm SD ($10^9/L$)	8.35 ± 3.11	3.73 ± 0.21	0.0001
Lymphocyte count mean \pm SD ($10^9/L$)	1.46 ± 5.9	1.78 ± 0.49	0.5895
CRP, mean \pm SD (mg/l)	37.11 ± 37.47	17.52 ± 32.17	0.0001
D-dimer, mean \pm SD (FEU ng/ml)	3271.87 ± 1052	854.03 ± 115.25	< 0.0001
NLR, mean \pm SD	11.75 ± 1.03	2.42 ± 0.43	< 0.0001

Table 1 shows baseline demographic and laboratory characteristics of the severe and non-severe COVID-19 patients. There were many significant differences in the parameters of baseline characteristics between the severe group and the non-severe group. The patients in the severe group had older average age (66 vs. 51 years; $p = 0.0046$). Compared with patients with non-severe COVID-19 infection, severe COVID-19 patients had higher levels of CRP, D-dimer, NLR, platelets, neutrophil count and lower levels of lymphocyte and hemoglobin.

The results showed that the median lymphocyte value of the severe patients was lower than that of the non-severe patients (1.48 vs $1.78 \times 10^9/L$; $P < 0.589$), while the median neutrophil value of the severe patients was quite higher than non-severe patients (8.35 vs $3.73 \times 10^9/L$; $P < 0.0001$). In addition, the median NLR value of the severe patients was dramatically higher than non-severe patients (11.75 vs 2.42 ; $P < 0.0001$). Plasma CRP levels were higher in severe cases than in the non-severe, and this difference was significant ($p = 0.0001$).

The NLR value equal to 5 was a boundary value worthy of reference, and more than 60% severe patients had an NLR value greater than 5 and over 93% non-severe patients had an NLR value less than 5. In the correlation analysis of NLR and CLR indices as inflammatory biomarkers in the COVID-19 patients, a positive correlation was observed between NLR values and CRP in the severe vs non-severe COVID-19 patients ($t = 4.61477$ vs $t = 4.92334$, $p \leq 0.00001$). NLR was also significantly correlated with D-dimer, hemoglobin and platelets in the severe vs non-severe COVID-19 patients ($t = 12.5638$, $t = 69.71364$, $t = 31.66096$ vs $t = 38.65221$, $t = 126.88709$, $t = 38.65221$, $p \leq 0.00001$).

In the presented Fig. 1 and Fig. 2 is seen the correlation between the NLR and CRP levels in the severe and non-severe COVID-19 patients.

DISCUSSION

As far as we know, this is the first study that investigates NLR and CRP as inflammatory biomarkers in severe and non-severe COVID-19 patients in North Macedonia. This study demonstrated that severe COVID-19 patients had significantly higher NLR, WBC, platelets, neutrophils and D-dimer values and lower hemoglobin and lymphocytes compared with the patients with non-severe COVID-19 infection.

In many studies, it has been observed that advanced age is the main factor in hospitalization risk. This study showed significant differences between the average age of the severe and non-severe cases

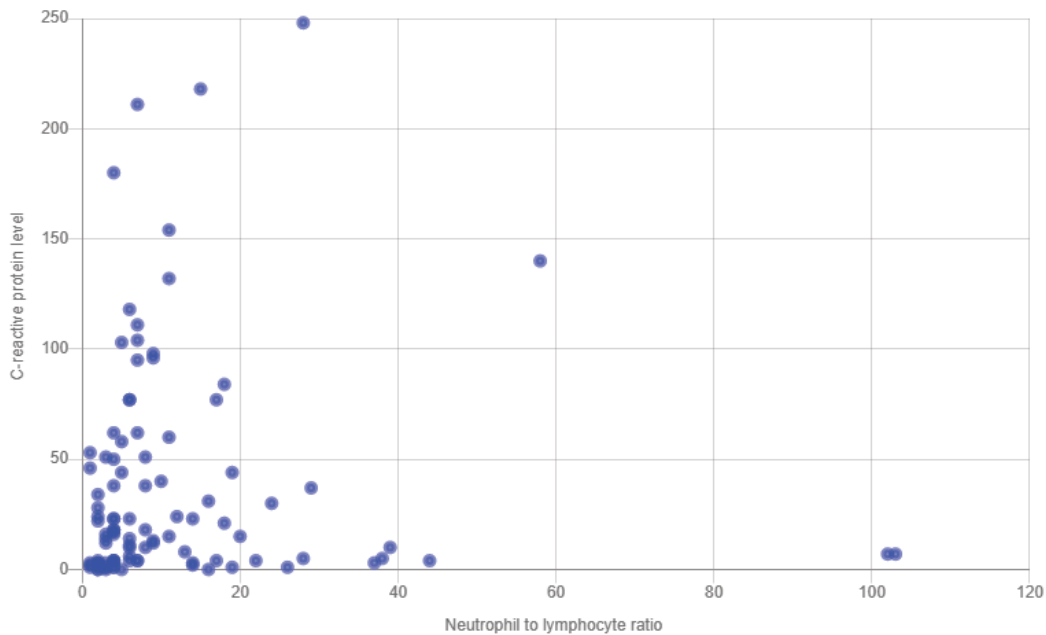


Fig. 1. Correlation between NLR with CRP levels in severe COVID-19 patients

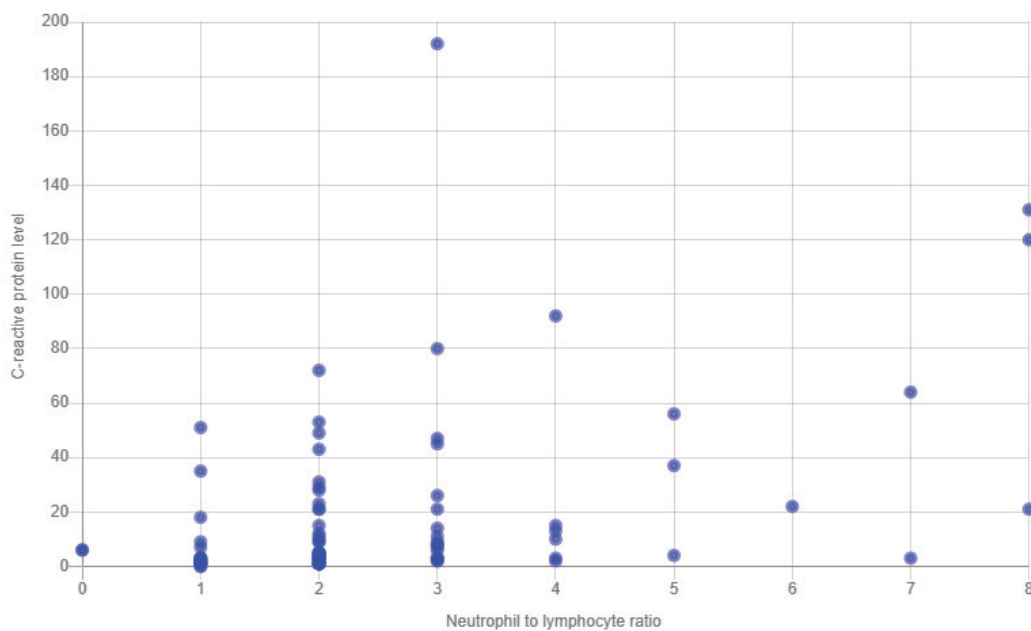


Fig. 2. Correlation between NLR with CRP levels in non-severe COVID-19 patients

(66.63 ± 49.49 vs. 51.45 ± 19.01 years; $p = 0.0046$). 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. [12, 13]. 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 inflammation), both characteristic of the elderly [14].

There is a positive relationship between NLR and CRP levels. Our results showed that increased NLR

is a sign of COVID-19 progress and can lead to more severe disease. Recently, NLR was extensively investigated for its role in assessing prognosis and severity of COVID-19 infection. In studies and meta-analyses on NLR-related COVID-19, it has been reported that high neutrophil count and decreased lymphocyte count and NLR are useful in predicting disease severity [15]. In a study, in which 548 COVID-19 cases were analyzed, it was reported that increased neutrophil count and NLR were found in critically ill patients and the cases with mortality, and low eosinophil, lymphocyte and platelet counts were observed during hos-

pitalization of these cases [16]. NLR is widely used marker and defined by neutrophil count divided by lymphocyte count. The NLR index was found to be an indicator of prognosis in patients with pneumonia and tumors [17]. The findings have proven the hypothesis of the present study and suggest that elevated NLR is a functional biomarker that influences the progression of infection with COVID-19. These findings are supported by previous studies that have backed up the prognostic utility of NLR in COVID-19 patients [12, 18]. Ding et al. [19] found that NLR index positively correlated with the length of hospital stay and has a role in predicting the prognosis of disease for COVID-19 patients. Another study reported an elevated NLR in non-survivors than survivors and the magnitude of rising was correlated with severity of illness. The relationship between NLR and infectious diseases is well-known. An explanation for this relationship may be that the neutrophil is a part of leukocytes that arises from the venous system and is transmitted to the immune system [20]. Neutrophils generate large amounts of reactive oxygen species and could save the cell from the virus by inducing DNA damage [21]. An excessive and uncontrolled cytokine production plays an important role in the pathogenesis of COVID-19 pneumonia. The virus enters the alveolar cells via angiotensin converting enzyme 2 receptors and triggers the release of inflammatory factors from the cells resulting in activation of macrophages in the alveolar tissue [22, 23]. The inducing factors and chemokines released from macrophages cause the accumulation of mononuclear cells in the lung tissue. Extreme infiltration of inflammatory cells induces a cytokine storm leading to acute lung injury and ARDS, the severe consequences of COVID-19 pneumonia [22].

Laboratory abnormalities such as decreased platelet, lymphocyte and increased neutrophil count and CRP level were reported in COVID-19 patients [24]. WBC and its differential counts including lymphocytes and neutrophils are associated with the inflammation and immune systems [25]. Platelets, which are anucleate blood cells produced from megakaryocytes in the bone marrow, play an important role in the host inflammatory and immune responses as well as regulation of hemostasis and thrombosis [26]. In the present study, we found that severe COVID-19 patients had lower lymphocyte and higher neutrophil counts and CRP levels than the non-severe group. Moreover, Li et al. [27]. reported that increased neutrophil percentage and CRP level and decreased lymphocyte counts were closely related to the severity of COVID-19 pneumonia. CRP, a positive acute phase

protein, is one of the markers reflecting the systemic inflammatory response of body [28]. Previous studies have shown that CRP levels can be used for the early detection of patients with pneumonia, which had higher levels of CRP than others [29]. In line with these findings, in this study, CRP levels were significantly correlated with disease severity. This means that CRP levels can be considered a warning factor for the progression of COVID-19. This study found that CRP concentration was significantly higher in the severe than non-severe cases. This finding is consistent with the results in the study of Qin et al. [30]. 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. In the current study, a significantly higher CRP level ($p = 0.0001$) was observed in severe COVID-19 patients compared with the non-severe group, as previously reported by other studies [9].

Continuous dynamic monitoring of reliable clinical and laboratory indicators will help identify a subset of patients with COVID-19 developing severe disease which can contribute to an early control of this disease and a good clinical prognosis. The results showed that the age of COVID-19 patients is an important factor influencing the development of a patient's condition. A routine blood test is easy to conduct almost in every hospital and medical testing laboratory, and among which, neutrophil and lymphocyte are two key indexes that are evidently affected by SARS-CoV-2 infection and demonstrated to be with significant differences in the severe and non-severe patients with COVID-19. NLR is calculated according to the specific value of neutrophil-to-lymphocyte, which can amplify the value of neutrophil and lymphocyte. Routine analyzes such as NLR and CRP and their integration can lead to improved prognosis and are therefore recommended as a valuable early marker for assessing prognosis and evaluating the severity of clinical symptoms in patients with COVID-19.

CONCLUSION

The COVID-19 pandemic continues to affect the world with increasing case and mortality rates. In this study, the correlation of leukocyte count, neutrophil absolute count, NLR and CRP with inflamma-

tory markers was determined. NLR and CRP were observed to be predictive in cases with hospitalization. Future studies are needed regarding the role of these biomarkers in the pathogenesis of the disease. Our results showed that NLR and CRP are significantly higher in patients with severe COVID-19, and they could be effective biomarkers in predicting COVID-19 severity.

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