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Prognostic Significance of Neutrophil-Lymphocyte ratio in COVID-19 Infection

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Research Article

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ABSTRACT

Objective: Serum markers, radiological signs and clinical findings may help guide the assessmentof the prognosis of COVID -19 infection.Neutrophil-lymphocyte ratio is a cheap and easily attainable inflammatory marker.This study aims to investigate whether neutrophil-lymphocyte ratio is associated with the clinical course of the disease in COVID-19 patients with the non-severe disease

Materials and Methods: We retrospectively analyzed the results of 189 patients who were followed-up at the pandemic clinic of Erciyes University, Medical Faculty Hospital. Patients were categorized according to the criteria released by the Republic of Turkey Ministry of Health. That guide classifies the patients as mild-moderate and severe.Patients over 18 years of age who were treated with COVID-19 and whose symptoms were not severe were included in this study.Patients who have missing data were excluded from this study.

Results: The findings showed that there was no significant difference in hospitalized patients concerning neutrophil-lymphocyte ratiolevels, white blood cell count, neutrophil count, lymphocyte count in mild or moderate COVID-19 infected patients at admission and discharge. There was a significant difference in CRP levels between admission and discharge however patients did not progress to a clinical deterioration on the follow-up.

Conclusion: Neutrophil-lymphocyte ratiolevels did not change significantly between admission and discharge in mild-moderate patients. In light of previous studies reporting that neutrophil-lymphocyte ratiolevels are high in patients with severe COVID-19, the present study suggest that neutrophil-lymphocyte ratio levels are a proper marker for predicting the tendency to severe COVID -19 disease in the follow-up of the patients.

Keywords: COVID -19 pandemic, COVID -19 infection,Neutrophil-lymphocyte ratio

COVID-19 İnfeksiyonunda Nötrofil-Lenfosit Oranının Prognostik Değeri

ÖZ

Amaç: Serum belirteçleri, radyolojik bulgular ve klinik bulgular COVID-19 infeksiyonunun prognozunu belirlemede kullanılmaktadır. Nötrofil-Lenfosit Oranı ucuz, kolay ulaşılabilir bir inflamasyon belirtecidir.Bu çalışmanın amacı klinik olarak hafif –orta şiddetli COVID-19 hastalarında nötrofil-lenfosit oranının hastalığın klinik seyri ile ilişkili olup olmadığını göstermektir.

Gereç ve Yöntemler: Bu çalışmada, Erciyes Üniversitesi Tıp Fakültesi Hastanesi pandemi kliniğinde takip edilen 189 hastanın sonuçlarını retrospektif olarak inceledik. Hastalar TC Sağlık Bakanlığı tarafından belirlenen kriterlere göre sınıflandırıldı. Bu rehbere göre hastalar hafif,orta ve şiddetli olarak sınıflandırılmaktadır. Çalışmaya COVID-19 ile tedavi edilen ve semptomları şiddetli olmayan 18 yaş üstü hastalar dahil edildi. Eksik verileri olan hastalar çalışma dışı bırakıldı.

Bulgular: Hastaneye yatırılan COVID-19 ile enfekte hafif - orta şiddettehastalarda hastaneye yatış ve taburculuk değerleri arasında nötrofil-lenfosit oranı, lökosit sayısı, nötrofil sayısı ve lenfosit sayısı açısından anlamlı bir fark yoktu. CRP düzeylerinde hastaneye yatış ve taburculuk değerleri arasında anlamlı bir fark bulduk.Çalışmaya alınan hastalarda klinik bir kötüleşmeye ilerleme izlenmedi.

Sonuç: COVID-19 ile enfektehafif –orta şiddette hastalarda hastaneye yatış ve taburculuk değerleri arasında nötrofil-lenfosit oranı düzeyleri arasında istatistiksel olarak anlamlı bir değişim görülmedi.Daha önce COVID-19 ile enfekteağır şiddette hastalarda nötrofil-lenfosit oranı seviyelerinin arrtığını gösteren çalışmaların ışığında; nötrofil-lenfosit oranı seviyelerinin COVID-19 ile enfektehastaların şiddetli hastalığa progresyonunu belirlemede faydalı bir belirteç olduğu sonucuna vardık.

Anahtar sözcükler: COVID -19 pandemisi , COVID -19 infeksiyonu , nötrofil-lenfosit oranı

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Introduction

The COVID -19 virus is a member of the coronaviridae family.It is transmitted human to human by droplets in the inhaled air, close contact with the infected patient, or touch to infected materials. Affected patients can be asymptomatic or symptomatic.Cough, dyspnea,fever, headache, myalgia, fatigue,malaise, and diarrhea are frequent symptoms in patients.

The main complications of theCOVID -19 virus are pneumonia, acute respiratory failure,and deterioration of multiple organs and systems [1].

In addition to these complications, COVID-19 may lead to different clinical consequences. Mithani et al, presented new-onset seizures and encephalopathy in severe COVID -19 patients [2]. Heart failure, myocardial injury, cardiomyopathy,coronary artery disease,the tendency to thrombosis or ECG changes are cardiac outcomes of COVID -19 disease[3-6]. COVID -19 also affects renal functions .Acute renal failure, clinical deterioration and increased mortality in chronic renal failure patients, electrolyte disturbances are prominent clinical results [7]. Recent studies showed that gastrointestinal system involvement in COVID -19 is not uncommon and emerges as pancreatitis, abnormal liver function enzyme levels[8-10].In addition,skin lesions may appear either related to the COVID -19 or drugs that are used in the treatment of the COVID -19 [11].

The incubation period of COVID -19 is approximately two weeks. Mortality rate is changing according to race and country. Factors thought to be potential determinants in predicting clinical course are age, comorbidities, creatinine,d-dimer, leukocytosis, lymphopenia and CT severity score [12]. There is no evidence-based specific and curative therapy for the COVID -19 virus.

Serum markers, radiological signs and clinical findings may help in guiding to assess the poor prognosis of COVID -19 infection. Lymphocyte and neutrophil count, neutrophil-lymphocyte ratio (NLR), C-reactive protein, erythrocyte sedimentation rate, procalcitonin, D-dimer, troponin, creatine kinase, aspartate aminotransferase (AST) and ferritin are supposed to be useful for this purpose[13].

NLR is a basic and easily accessible parametric quantity that determines the severity ofinflammation[14]. Additionally, NLR is also beneficial in predicting prognosis, morbidity, mortality, and treatment response in coronary artery diseases, several cancers, transplant patients, systemic inflammatory diseases and infectious diseases.In a study investigating the relationship between NLR and acute coronary syndrome, Dong et al. have found that high NLR levels are related to poor prognosis. Additionally, it has been reported that survival is low in patients with ovarian, gastric, and breast cancer with high NLR levels.Hammad et al. showed that although NLR is not associated with neurological and ocular deficits, it is associated with disease activity and skin manifestations in patients with Behcet's disease [15-18].

In this study, we aimed to show whether NLR is associated with the clinical course of the disease in COVID-19 patients with non-severe disease.

Materials and Methods

We retrospectively analyzed the results of 189 patients who were followed-up at the pandemic clinic of Erciyes University, Medical Faculty Hospital between March-August 2020. Diagnosis of COVID-19 was made, using nucleic acid amplification tests (polymerase chain reaction (PCR) with throat and nose swaps (Xian Galaxy Rising Industrial, China) or serologically with COVID-19 rapid antigen (Hotgen Biotech Co. Ltd, China) or radiologically computed thorax tomography findings. Patients were categorized according to the criteria released by the Republic of Turkey Ministry of Health. That guide classifies the patients as mild-moderate and severe.Proposed severe disease indexes were dyspnea and respiratory distress (Respiratory rate of ≥ 30 / min, PaO2 / FiO2 <300, SpO2 <90% or PaO2 <70 mmHg despite 5 L / min oxygen therapy), hypotension (systolic blood pressure <90 mmHg and 40 mmHg decrement from usual SBP and mean arterial pressure <65 mmHg, tachycardia> 100 / min, acute kidney damage, acute liver function test disturbances, confusion, unidentified acute bleeding diathesis, development of acute organ dysfunction, patients with immunosuppression, increased troponin levels, arrhythmia, and lactate> 2 mmol.More than one criteria are accepted as severe diseases.

Patients over 18 years of age who were treated with COVID-19 and whose symptoms were not severe were included in this study. Patients who had missing data were excluded from this study. Besides, due to patients who had high severity indexes were treated in the intensive care unit, those patients could not be included in this study. We did not able to access to the patients that admitted to the intensive care unit for that reason we can not include this patients to the study .

Patients received treatment during the follow-upunder the guidelines of the COVID-19 published bythe Republic of Turkey Ministry of Health for COVID-19 pandemic services.

Data regarding the demographic features and laboratory results of the patientswere collected from the hospital database.The neutrophil-lymphocyte ratio was calculated by dividing neutrophil count by lymphocyte count. All analyses were performed using SPSS 24.0 statistics software for Windows.

This study was approved by the Local Ethics Committee of Sivas Cumhuriyet University (Number:2020/318, date:24.06.2020).

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Table 1. Proposed Severe Disease Indexes

1-Respiratory distress :
- **Respiratory rate of≥ 30 / min**
- **PaO2 / FiO2 <300**
- **SpO2 < 90%, PaO2 <70 mmHg despite 5 L / min oxygen therapy**

2-Cardiac Disfunction:
- **Systolic blood pressure(SBP)<90 mmHg or**
- **40 mmHg decreament from usual SBP or**
- **Mean arterial pressure <65 mmHg**
- **Tachycardia> 100 / min**
- **Arrhythmia**

3-Acute organ dysfunction(liver/kidney)
4-Confusion/Coma
5-Unidentified Acute Bleeding Diathesis
6-Immunosupression
7-Lactate >2 mmol

Statistical analysis

The compliance of the data to normal distribution was evaluated by the histogram, q-q graphs, and Shapiro-Wilk test. Variance homogeneity was tested with the Levene test. The dependent sample t-test and the Wilcoxon test were used to compare the variables measured at admission and discharge. The significance level was accepted as p <0.05.

Results

Our study included189 patients (Age: 55.95±17.62 years old), 70 of whom were females(37 %), and 119 of whom were males (63 %).Distribution of the comorbidities among patients were as follows : Diabetes mellitus 50(26.5 %), hypertension 65(34.4 %), ischemic heart disease24 (12.7%), cirrhosis 2 (1.1%),non alcoholic steatohepatitis 1(0.5 %), viral hepatitis 3 (1.6%), chronic renal disease 23(12.2 %), chronic obstructive pulmonary disease 10 (5.3%), other diseases 40(21.2%) .The fever of the patients had a distribution of 36.7 ± 0.8 C°. Systolic blood pressure distribution was 126.64 ± 36.34 mmHg ;diastolic blood pressure distribution was 76.08 ± 19.37 mmHg; pulse distribution was 103.57 ± 21.34 beets per minute. The mean respiratory rate was 30.38 ± 7.46 breaths per minute and the mean saturation was 90.94 ± 10.43 percent.

Complete blood count results in the first day of hospitalization were as follows Hb: 13.19±2.34 mg /dl, hematocrit 38.85±8.49 %, white blood cell count :6470 cells / µL (min:4800-max :9910),neutrophil count 4245 cells / µL (min :2895-max:7295), lymphocyte count 1420 cells / µL (min: 955 – max :1880), eosinophil count 20 cells / µL (min:10- max :80), platelet count : 273.5 x10^3/ µL(min:191500-max:287500), mean platelet volume 10.49±0.97, NLR 2.98 (min:1.71- max :6.78), C-reactive protein 22.0(6.0-84.0) mg/L .The values after discharge were Hb: 11.94±2.70 mg /dl, hematocrit 32.43±7.78 %, white blood cell count : 6480 cells / µL (min: 5000-max : 9520), neutrophil count 3980 cells / µL (min : 2790-max: 7580), lymphocyte count 1450 cells / µL (min: 870 – max : 1980), eosinophil count 50 cells / µL (min:15- max: 120), platelet count : 291.5x10^3/ µL (min: 197500-max:295 500), mean platelet volume 10.49±1.02, NLR 2.8 (min:1.74-max :6.62), C-reactive protein 16.0(3.3-61) mg/L.

Table 2: Complete blood cell and C-Reactive Protein levels on Admission and Discharge

Variables		Admission	Discharge	*p*
WBC	(cells / µL)	6470(4800-9910)	6480(5000-9520)	0.775
Platelet	(x10^3/ µL)	273.5(191.5-187500.0)	291.5(197.5-209500.0)	**0.002**
Hemoglobin	(mg /dl)	13.19±2.34	11.94±2.70	**<0.001**
Hematocrit	(%)	38.85±8.49	32.43±7.78	**<0.001**
Neutrophyl	(cells / µL)	4245.0(2895.0-7295.0)	3980.0(2790.0-7580.0)	0.733
Lymphocyte	(cells / µL)	1420.0(955.0-1880.0)	1450.0(870.0-1980.0)	0.848
NLR		2.98(1.71-6.78)	2.80(1.74-6.62)	0.780
Eosinophil	(cells / µL)	20.0(10.0-80.0)	50.0(15.0-120.0)	**<0.001**
MPV	(fl)	10.49±0.97	10.49±1.02	0.951
C-reactive protein	(mg/L)	22.0(6.0-84.0)	16.0(3.3-61.0)	**0.026**

WBC:White blood cell **NLR**: Neutrophil/Lymphocyte**MPV:** Mean Platelet Volume

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Discussion

We found no significant difference in hospitalized patients concerning NLR levels, white blood cell count, neutrophil count, lymphocyte count, mean platelet volume in mild or moderate COVID-19infected patients.However, we found a significant difference in Hemoglobin, Hematocrit, Eosinophil, Platelet and CRP levels.

Studies have been conducted to show the association between NLR levels with the outcomes, morbidity, and prognosis of COVID-19. These studies were predominantly conducted in severe COVID-19 patients. Ma et al conducted a study to show the neutrophil-to-lymphocyte ratio as a predictive biomarker for moderate-severe ARDS in severe COVID-19 patients. In this study,they revealed that NLR is a substantial marker in recognizing the severity of COVID-19 patients[19]. In contrast to these study, the disease severity was mild to moderate in the patients in our study.In another studies that patients who were not classified according to the severity of the disease, Liu et al.showed that NLR is an independent predictor of in-hospital mortality in COVID-19 infection[20]. Jimeno et al and Yang et al concluded that NLR is a useful marker for determining the prognosis in both severe and non-severe COVID-19 disease[21]. Additionally, a previous study conducted by Fu et al in different countries found that NLR is a prognostic biomarker and differentiates severe disease from non-severe disease [22].Similar to these studies, our study showed that the absence of change in neutrophil-lymphocyte ratios in patients followed up with COVID -19 is a sign for the clinician that the disease does not tend to exacerbate. In a recent study from Turkey which compares COVID -19 positive and COVID -19 negative patients, Nalbant et al elucidated that COVID -19 positive patients have high NLR levels than COVID -19 negative patients [23]. Different from our study, these study patients did not categorize according to the severity index. The mechanism behind the increased NLR levels during COVID-19 infection can be explained in two ways: neutrophil levels increase to respond to the viral infection and coronavirus targets and destroys the lymphocytes due to the ACE2 receptors on the surface of these cells [24].

In our study, we found a significant difference between hospitalization and discharge values of CRP. We determined that CRP is a useful marker for predicting the non –severe COVID-19 infection course. Former studies concluded that CRP is a useful marker in assessing prognosis in both severe and non-serious diseases [25].

Our study has some limitations. We retrospectively analyzed only mild-moderate COVID-19 infected patients. We excluded severe COVID-19 infected patients. Thus, we could not be able to make a comparison between mild/moderate and severe patients.

Inpatients with mild-moderate COVID -19 disease, NLR levels show a stable pattern. We conclude that NLR levels are a proper marker for predicting the tendency to severe COVID -19 disease in the follow-up of mild-moderate patients.

Conflict of Interest Disclosure: The authors declare that there are no conflicts of interest.
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