



New Markers in the Differentiation of Covid 19 Disease and Pneumonia: Neutrophil and Platelet Lymphocyte Ratio

Covid 19 Hastalığında, Pnömoninin Ayırt Edilmesinde Yeni Belirteçler: Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranı

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Abstract

Background: COVID-19 is a disease that starts like a simple upper respiratory infection and causes pneumonia and severe respiratory failure. Due to cytokine storm and hyperinflammation, some hematological and biochemical findings appear in the course of the disease. Complete blood count (CBC) is a very simple and inexpensive test that can be used in many infectious diseases.

Material and Method: Eighty patients diagnosed with COVID-19 by RT-PCR were divided into two groups according to the presence of pneumonia in the thorax CT (CT + 40 patients and CT- 40 patients). Forty healthy patients who had no previous disease were selected as the control group. The demographic and laboratory characteristics of COVID-19 patients with and without pneumonia in all three groups and control group patients were compared retrospectively.

Results: While there was a significant difference between the COVID-19 group and the control group in terms of neutrophil lymphocyte ratio (NLR) and mean platelet volume (MPV), no differences were observed in COVID patients with and without pneumonia in terms of NLR and MPV. There was no significant difference between the COVID-19 group and the control group and the COVID pneumonia group in terms of Platelet lymphocyte ratio (PLR).

Conclusion: NLR and MPV can be used as diagnostics for the diagnosis of COVID-19 disease, while PLR cannot be used. However, NLR and MPV values are not significant in evaluating COVID pneumonia and disease severity.

Keywords: COVID-19, SARS-CoV-2, pneumonia, neutrophil lymphocyte ratio, platelet lymphocyte ratio, mean platelet volume, MPV, NLR, PLR

Öz

Arka Plan: COVID-19; Basit bir üst solunum yolu enfeksiyonu gibi başlayıp zatürreye ve ciddi solunum yetmezliğine neden olan pandemik bir hastalıktır. Hastalıkta sitokin fırtınası ve hiperinflamasyon nedeniyle bazı hematolojik ve biyokimyasal bulgular ortaya çıkar. Tam kan sayımı (CBC), birçok bulaşıcı hastalıkta kullanılabilen çok basit ve ucuz bir testtir.

Gereç ve Yöntem: RT-PCR ile COVID-19 tanısı alan 80 hasta toraks BT'de pnömoni varlığına göre iki gruba ayrıldı (CT + 40 hasta ve CT- 40 hasta). Kontrol grubu olarak daha önce hastalığı olmayan 40 sağlıklı gönüllü seçildi. Her üç gruptaki pnömonili ve pnömonisiz COVID-19 hastaları ile kontrol grubundakilerin demografik ve laboratuvar özellikleri retrospektif olarak karşılaştırıldı.

Bulgular: COVID-19 grubu ile kontrol grubu arasında nötrofil lenfosit oranı (NLO) ve ortalama trombosit hacmi (MPV) açısından anlamlı fark varken, pnömonili ve pnömonisiz COVID hastalarında NLO açısından farklılık gözlenmedi. Platelet lenfosit oranı (PLR) açısından COVID-19 grubu ile kontrol grubu ve COVID pnömoni grubu arasında anlamlı fark yoktu.

Sonuç: NLR ve MPV, COVID-19 hastalığının teşhisi için tanı olarak kullanılabilirken, PLR kullanılamaz. Bununla birlikte, NLR ve MPV değerleri COVID pnömonisi ve hastalık şiddetinin değerlendirilmesinde anlamlı değildir.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, pnömoni, nötrofil lenfosit oranı, trombosit lenfosit oranı, NLR, PLR, MPV



INTRODUCTION

COVID-19 disease is a serious infectious disease that started in Wuhan, China in December 2019 and influenced the whole world and was accepted as a pandemic by the World Health Organization (WHO) in March 2020, affecting both upper and lower respiratory tract.^[1] Virus causes acute respiratory failure such as serious acute respiratory failure virus (SARS) in 2002-2003 and middle east respiratory syndrome virus (MERS) in 2012-2013. The incubation period of the disease is 2-14 days. Symptoms begin at the latest after this period. The most common symptoms are fever, cough, respiratory failure, loss of smell and taste, and recently increasing complaints of diarrhea.^[2] As of July 2020, approximately 10,000,000 new cases and nearly 500,000 deaths have been reported.^[3] Although the first transition of the disease was determined as animal-human, its fastest spread was in the form of human-human. The disease begins with the intake of aerosols from the respiratory tract. The virus, which is primarily located in the nasopharynx, descends to the lung in time. It causes accumulation of fluid in the alveoli in the lung, leading to the appearance of ground glass on tomography. Therefore, it leads to acute respiratory failure.^[4,5]

In COVID-19 disease, diagnostic haematological parameters were determined. The most commonly defined parameters are lymphopenia, leukocytosis, neutrophilia, thrombocytopenia, D-Dimer height, C-Reactive protein (CRP) height, PT-INR height Troponin increase, Lactate Dehydrogenase height (LDH).^[2,6-8] Complete blood count (CBC) is a fairly simple, practical and inexpensive test.

Neutrophil-lymphocyte ratio, Platelet lymphocyte ratio and mean platelet volume can be used in COVID-19 as well as in other diseases.^[9,10] In our study, hematology parameters of PCR positive patients with and without COVID-19 will be compared.

MATERIAL AND METHOD

For this study, 80 patients diagnosed with COVID-19 and 40 healthy volunteers at our center between March 2020 and June 2020 were used. All patients were evaluated retrospectively. Patients with COVID-19 were divided into two groups as CT + and CT- according to the presence of pneumonia in Thorax CT. The patients were divided into three groups as control, PCR + CT- and PCR+ CT+

COVID-19 patients in the study consisted of patients diagnosed with Polymerase Chain Reaction (PCR) with the symptoms such as fever, weakness, myalgia, shortness of breath, cough, diarrhea, and loss of taste. Nasopharyngeal and throat swabs (combined swabs) were taken from the patients and evaluated by PCR. The diagnosis of PCR was made with Applied Biosystems GeneAmp® PCR System 9700 device (Thermo Fisher Scientific, USA). Thorax CT was also performed in patients diagnosed with COVID-19 by PCR, and the patients were called CT + and CT-. For the control

group, 40 healthy volunteers were selected in our center for various reasons and without chronic or acute infectious diseases. Laboratory values of 40 patients in PCR + CT-, PCR + CT + and control group were evaluated retrospectively. Leukocyte (WBC), hemoglobin, hematocrit, mean platelet volume (MPV), neutrophil, lymphocyte count, C-reactive protein (CRP), sedim and procalcitonin values were calculated in the patients' complete blood count (CBC) and biochemistry tests. In addition, neutrophil lymphocyte ratio and platelet lymphocyte ratio were calculated according to these values. These values were compared for all three groups.

Covid-19 diagnosis and treatment for the Republic of Turkey Ministry of Health Science Board has benefited from Covidien-19 guidelines. Accordingly, patients with complaints such as fever, weakness, joint pain, headache, shortness of breath, cough, smell and taste disorder, diarrhea were taken by nasopharyngeal swab in the isolation rooms and PCR device was diagnosed and the patients who had SARS-CoV-2 virus were identified. Thorax CT was taken to evaluate the presence of PCR + lung pneumonia. CT examinations (MSCT, Philips Brilliance ICT 256; Philips Medical Systems, Netherlands) were performed with the device (512x512matrix, voltage 100 kV, current 150 mAs). Those with consolidation and ground-glass area in tomography were evaluated as pneumonia. In treatment, Hydroxychloroquine tablet 2 * 200 mg (5 days) and Enfluvir tablet (2 * 75 mg tablet 5 days) were given to all patients. Those with severe pneumonia and favipravir areas were excluded from the study.

In addition, these patients were evaluated in terms of age, gender, smoking, additional disease, and severity of disease. The degree of the disease; 1) Mild (no pneumonia or mild pneumonia), 2) Moderate (dyspnea, hypoxia or severe progression in lung findings within 24 hours), 3) Severe (Respiratory Failure, Shock, Multi-Organ Failure). Afyonkarahisar Health Sciences University for Non-Interventional Studies from the Clinical Research Ethics Committee (07.11.2020/2020-7) and the Commission for Scientific Research from the Ministry of Health of the Republic of Turkey (04/29/2020) has been allowed us to carry out the study. The study was carried out in accordance with the Declaration of Helsinki.

Statistical Analysis

All values are calculated as mean \pm standard deviation. The data obtained were evaluated with descriptive statistics (Arithmetic mean, median, standard deviation, percentage distributions). When comparing the mean between groups, the normal distribution suitability was first evaluated by the Kolmogorov Smirnov and Shapiro Wilk tests. When comparing the percentage distributions of categorical data between groups, Chi Square test and one way anova were used. SPSS 22.0 (IBM SPSS Statistics, Chicago, USA) was used for data analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Of the 120 people who participated in our study, 80 (66.66%) were PCR positive Covid 19 and 40 (33.33%) were healthy people with no chronic disease.

When the hemogram values of the participants in our study were evaluated, the WBC results of COVID-19 PCR + patients were 6.01 (2.72-12.46) $10^3/\text{ul}$ and 7.35 (4.73-15.35) $10^3/\text{ul}$ in the control group. and there was a statistically significant difference ($p < 0.001$). Considering neutrophil values, COVID-19 PCR + was 1.52 (0.49-49.48) $10^3/\text{ul}$ in the control group and 2.00 (0.78-5.41) $10^3/\text{ul}$ in the control group ($p < 0.001$) In terms of eritocyte distribution volume ratios (RDW), COVID-19 was 18.80 (11.40-24.20)% in PCR + patients, while it was 13.15 (11.70-18.80) in the control group ($p = 0.011$). When evaluated in terms of mean platelet Volume (MPV) values, COVID- 19 was 10.12 (8.10-13.40) in PCR + patients and 9.30 (8.00-10.90) in the control group ($p < 0.001$). In terms of reactive protein (CRP) values, COVID-19 was 2.80 (0.00-195.40) mg/l in PCR + patients and 0.80 (0.00-59.30) mg/l in the control group. ($p = 0.049$) (Table 1 and 2).

When neutrophil/lymphocyte ratio (NLR) and Platelet/lymphocyte ratio (PLR) ratios were evaluated, there was no statistically significant difference in terms of PLR rates ($p = 0.334$, $p = 0.026$ respectively) (Table 2)

When the comparison of NLR and PLR ratios between two groups was evaluated in our study, there was a statistically significant difference between the group with PCR + thorax bt - and thorax bt and healthy individuals without disease clinic in terms of NLR rates. When CT positive and negative groups were compared, there was no significant difference in terms of both NLR and PLR (Table 2).

When 40 patients with positive PCR and thorax bt were evaluated, the most common 27 (67.5%) right lung lower lobe, 23 (57.5%) left lung lower lobe, 13 (32.5%) right lung middle lobe, 11 (27.5%) was the right upper lobe of the lungs, 9 (22.5%) was the left lung upper lobe and 8 (20%) was the left lung lingula, and it was observed that it was observed most commonly in the right lung lower lobe (Picture 1).

Table 1. Laboratory variables of patients and control group

Laboratory values	COVID-19 (N=80)	Control (N=40)	P value
WBC ($10^3/\text{ul}$)	6.01 (2.72-12.46)	7.35 (4.73-15.35)	$P < 0.01$
Hemoglobin (g/dl)	13.84 \pm 1.57	13.80 \pm 1.72	0.905
RDW (%)	18.80 (11.40-24.20)	13.15 (11.70-18.80)	0.011
Platelet ($10^3/\text{ul}$)	258.02 (95.0-811.0)	249.50 (73.00-483.00)	0.286
MPV (Mean Platelet Volume)	10.12 (8.10-13.40)	9.30 (8.00-10.90)	$P < 0.01$
Prokalsitonin (ng/ml)	0.23 (0.12-0.68)	0.23 (0.00-0.37)	0.909
Hematocrit (%)	41.85 (32.80-409.00)	41.75 (23.60-50.10)	0.674
Neutrophil ($10^3/\text{ul}$)	3.26 (1.02-8.16)	4.57 (2.32-9.56)	$P < 0.01$
Lymphocytes ($10^3/\text{ul}$)	2.15 (0.86-4.96)	2.47 (1.03-5.94)	0.090
CRP (mg/l)	2.80 (0.00-195.40)	0.80 (0.00-59.30)	0.049
Sedimentasyon	5.16 \pm 9.02	4.35 \pm 7.26	0.791
Neutrophil lymphocyte ratio (NLR)	1.52 (0.49-6.48)	2.00 (0.78-5.41)	0.026
Platelet lymphocyteratio (PLR)	105.11 (39.92-375.21)	106.89 (56.10-276.00)	0.347

Table 2. Descriptive and laboratory variables of all groups

Laboratory values	COVID 19 (PCR+, CT+) N:40	COVID 19 (PCR+, CT-) N:40	Control N:40	P value
Age	44.45 \pm 11.77	36.20 \pm 15.57	43.50 \pm 14.68	0.019
WBC ($10^3/\text{ul}$)	6.57 (2.95-12.46)	5.54 (2.72-10.68)	7.35 (4.73-15.35)	$P < 0.01$
Hgb (g/dl)	13.74 \pm 1.61	13.94 \pm 1.53	13.80 \pm 1.72	0.848
RDW (%)	13.00 (11.40- 24.20)	12.75 (11.50-14.90)	13.15 (11.70-18.80)	0.011
Platelet ($10^3/\text{ul}$)	243.00 (95.00-811)	220.50 (151.00-454.00)	249.50 (73.00-483.00)	0.05
MPV	9.95 (8.20-13.40)	9.95 (8.10-12.70)	9.30 (8.00-10.90)	$P < 0.01$
Prokalsitonin (ng/ml)	0.24 (0.12-0.68)	0.22 (0.16-0.43)	0.23 (0.00-0.37)	0.216
Hematocrit (%)	41.60 (32.80-398.00)	41.90 (34.50-409.00)	41.75 (23.60-50.10)	0.827
Neutrophil ($10^3/\text{ul}$)	3.58 (1.29-8.16)	2.82 (1.02-7.08)	4.57 (2.32-9.56)	$P < 0.01$
Lymphocytes ($10^3/\text{ul}$)	2.24 (1.11-4.87)	2.02 (0.86-4.96)	2.47 (1.03-5.94)	0.05
CRP (mg/l)	4.55 (0.00-195.40)	1.55 (0.10-24.50)	0.80 (0.00-59.30)	0.001
Sedim	6.45 \pm 11.11	3.87 \pm 6.17	4.35 \pm 7.26	0.957
Neutrophil lymphocyte ratio (NLR)	1.52 (0.53-5.14)	1.53 (0.49-6.48)	2.00 (0.78-5.41)	0.068
Platelet lymphocyte ratio (PLR)	109.76 (46.82-315.56)	103.25 (39.92-375.21)	106.89 (56.10-276.00)	0.599

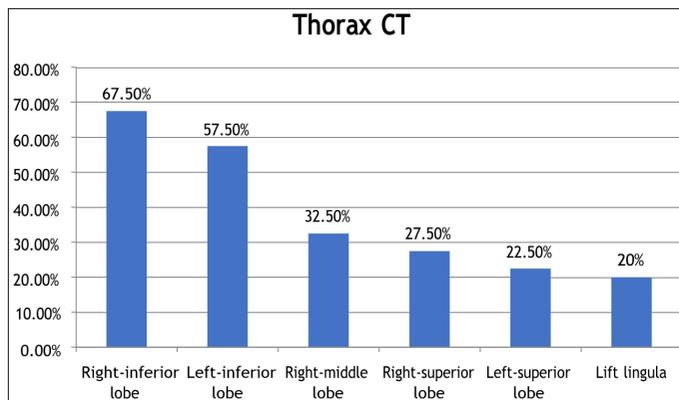


Figure 1. Frequency of lung lobe involvement in PCR + Thorax CT + patients

1. Hemogram is a simple and inexpensive test that can be easily applied anywhere.
2. NLR and MPV can be used in the diagnosis of Covid-19 disease, PLR has no diagnostic significance. While MPV increases in Covid-19 disease, NLR decreases.
3. In terms of NLR and MPV values, no significant difference was observed in patients with Covid-19 pneumonia compared to those who did not develop the disease.

DISCUSSION

COVID-19 disease is a viral infection disease caused by SARS-CoV-2 virus, which started in December 2019 in Wuhan, China, causing acute respiratory failure and coagulopathy in the organs, affecting the lung, which affected Europe and America in the first months of 2020. The disease begins as a simple upper respiratory tract infection by clinging to the respiratory tract via droplets. They descend to the lung in a short time and cause pneumonia. The disease forms ground-glass areas with Thorax CT. This image is typical for COVID-19 pneumonia. The disease then begins to cause diffuse alveolar damage. Disease diagnosis; The nasopharynx is placed by PCR by swab from the oropharynx or bronchoalveolar lavage. There is an increasing number of studies showing that CT is also diagnostic in PCR-patients.^[4,11,12]

PCR gold is the standard in the diagnosis of COVID-19. Sensitivity and specificity of laboratory values are not very high. However, certain values may assist in prognosis and treatment in the diagnosis and follow-up of COVID-19. Certain hematological parameters in COVID-19 patients have also been diagnostic. The most common laboratory finding in these patients is lymphopenia.^[6] The virus is thought to disrupt the immune response. In many studies, lymphopenia rates have been

defined between 35 and 75%. This rate increased as the severity of the disease increased. The rate of lymphopenia was very low in children with mild patients, in which the immune matter was less impaired.^[7] In most studies, the lymphocyte count has been defined below $<1.0 \times 10^9/L$.^[8] In our study, the lymphocyte count was $2.15 \times 10^9/L$, which was above the values

of COVID-19 patients in the literature. However, in our study, it may be related to the very low number of patients with severe COVID-19.

Similar to the information in the literature, hemoglobin values were evaluated as reference range in our study. Leukocytosis is seen in the case of a bacterial infection or superinfection in COVID-19 disease. In a study in the literature, it was stated that leukocytosis was seen in 11.4% of severe patients.^[7] In our study, although the leukocyte count was significantly lower than the control group, it was evaluated in the normal range. Although neutrophil count is expected to increase due to cytokine storm and hyperinflammation in infection, it remained in normal range in our study. However, their number has decreased significantly compared to the control group.

Reduced platelet counts (thrombocytopenia) is an expected condition in many viral diseases. A reduction in COVID-19 patients can also be expected. Both thrombocytopenia and mean platelet volume (MPV) have been used as a prognostic indicator in many diseases and sepsis.

Thrombocytopenia was used especially as a marker of hypoxemia.^[13,14] In our study, platelet counts were monitored similarly to the control group, and MPV values were significantly increased compared to the control group. Platelet counts were significantly higher in CT- compared to CT+, and MPV values did not change in the presence of pneumonia.

In addition to hemogram findings, biochemical markers can also be used in the diagnosis and follow-up of COVID-19. The most important of these are values such as C-reactive protein (CRP), procalcitonin, LDH. CRP is produced in the liver and used as an acute phase reactant. Viral inflammation also increases.^[15] In our study, it was found to be higher compared to the control group. Procalcitonin hormone is a prehormone with calcioma precursor and plays an important role in calcium metabolism. They show poor prognosis by increasing in sepsis and intense inflammation.^[16] In our study, no significant difference was observed between the control group and tomography positivity.

Neutrophil lymphocyte ratios (NLR), platelet lymphocyte ratios (PLR) and MPV (mean platelet volume) are used in the diagnosis and follow-up of many diseases.^[17,18] There are many studies related to these values in the literature.^[19,20] In many diseases, its predictive and prognostic value is important. In our study, NLR decreased in patients with COVID-19 compared to the control group, but did not change significantly with the presence of pneumonia. In a China-based study, it was stated that NLR values can be used to assess the severity of COVID-19 disease.^[21] Neutrophil lymphocyte values were

investigated in community-acquired pneumonias, and no relationship was observed between disease grade and values.^[22,23] PLR did not differ significantly from the control group. Therefore, based on our conclusions, NLR of COVID-19 patients is important in diagnosis and follow-up. However, its relation with the development of pneumonia and disease degree could not be determined. PLR has been used in many

diseases in the literature, but according to our observation, it has been understood that it will not be suitable as a marker in COVID disease and COVID pneumonia.

CONCLUSION

Neutrophil lymphocyte ratios are important in the diagnosis of COVID-19, but the significance of NLR values was not found in the development of pneumonia. Platelet lymphocyte ratio (PLR) is not considered as useful in the diagnosis of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received from Afyonkarahisar Healty Science University Clinical Research Ethic Committee (2020/7).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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