Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2022;47(2):526-534
DOI: 10.17826/cumj.996482

ARAŞTIRMA / RESEARCH

Association of hematological indices with neurological symptoms in COVID 19 patients

COVID 19 hastalarında hematolojik indekslerin nörolojik semptomlarla ilişkisi

SelmaTekin[1], Zeynep Ünlütürk[1], Çağdaş Erdoğan[1], Esin Avcı[2], Tuğba Sarı[3], Seçil Deniz[3], Hülya Aybek[2], Erhan Uğurlu[4], Murat Seyit[5], İsmail Hakkı Akbudak[6]

[1]Pamukkale University, Faculty of Medicine, Department of Neurology, [2]Department of Clinical Biochemistry, [3]Department of Infectious Diseases and Clinical Microbiology, [4]Department of Chest Diseases, [5]Department of Emergency Medicine, [6]Department of Internal Medicine, Denizli, Turkey

Cukurova Medical Journal 2022;47(2):526-534

Abstract

Purpose: The aim of this study was to compare the neurological involvement in Coronavirus 19 (COVID-19) patients with laboratory findings with these cost-free, practical tests.

Materials and Methods: Of the 170 patients diagnosed COVID-19, 103 patients could be reached by phone, and neurological symptoms were recorded as three categories. Laboratory tests of the patients and 103 controls whose real-time polymerase chain reaction (RT-PCR) test negative without any chronic disease history and drug use were obtained from the hospital software.

Results: White blood cell, neutrophil, lymphocyte, eosinophil, basophil, platelet were lower, monocyte to lymphocyte ratio and platelet to lymphocyte ratio higher in patients than controls. In the group with central nervous system findings, red blood cell and hematocrit counts, in the group with peripheral nervous system findings, lymphocyte and platelet counts and with sleep disturbances and muscle pain group eosinophil counts were lower in patients than those without.

Conclusion: COVID-19 patients with neurological symptoms have some hematological abnormalities. The presence of certain hematological findings may be a clue to the emergence of neurological symptoms, and early detection and correction of these hematological abnormalities may be the solution to prevent the development of neurological symptoms in COVID-19.

Keywords:. COVID-19, neurological symptom, hematological parameters, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, platelet to lymphocyte ratio

Öz

Amaç: Bu çalışmada, Coronavirüs 19 (COVID-19) hastalarında nörolojik tutulumu laboratuvar bulguları ile karşılaştırmayı ve bu maliyetsiz, pratik testlerin prognozu öngörelebilirliğini değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: COVID-19 tanısı konan 170 hastanın 103'üne telefonla ulaşılabildi ve nörolojik semptomlar üç kategoride kaydedildi. Herhangi bir kronik hastalık öyküsü ve ilaç kullanımı olmayan gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) testi negatif olan 103 hasta ve 103 kontrolün laboratuvar testleri, hastane yazılım programından elde edildi.

Bulgular: Hastalarda kontrollere göre lökosit, nötrofil, lenfosit, eozinofil, bazofil, trombosit sayıları daha düşük, monosit/lenfosit oranı ve trombosit/lenfosit oranı daha yüksekti. Santral sinir sistemi bulguları olan grupta eritrosit ve hematokrit sayıları, periferik sinir sistemi bulguları olanlarda lenfosit ve trombosit sayıları ile uyku bozukluğu ve kas ağrısı olan grupta eozinofil sayıları olmayanlara göre daha düşüktü.

Sonuç: Nörolojik semptomları olan COVID-19 hastalarında bazı hematolojik anormallikler saptandı. Bazı hematolojik bulguların varlığı, nörolojik semptomların ortaya çıkması için bir ipucu olabilir ve bu hematolojik anormalliklerin baştan saptanıp düzeltilmesi, COVID-19'da nörolojik semptomların gelişimini engellemek açısından çözüm olabilir.

Anahtar kelimeler: COVID-19, nörolojik semptom, hematolojik parametreler, nötrofil lenfosit oranı, monosit lenfosit oranı, platelet lenfosit oranı

Yazışma Adresi/Address for Correspondence: Dr. Selma Tekin, Pamukkale University, Faculty of Medicine, Department of Neurology, Denizli, Turkey E-mail: selmabilgintekin@gmail.com
Geliş tarihi/Received: 20.09.2021 Kabul tarihi/Accepted: 14.03.2022

INTRODUCTION

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in a patient working at a local indoor seafood market in Wuhan, Hubei Province, China[1]. The World Health Organization (WHO) announced on January 31, 2020 that this infection was an alarming international epidemic. This infection, which is highly contagious, spread all over the world rapidly. The first case of COVID-19 in a patient who had returned to Turkey after visiting from Europe was reported in Turkey on March 11, 2020[2]. Symptoms vary from asymptomatic infection to critical disease. The most common clinical findings include symptoms involving the upper respiratory tract, such as fever, cough, sore throat, and fatigue. But there have also been clinical findings related to other systems, such as the hematological, gastrointestinal, urinary, and neurological systems[3]. Neurological symptoms are also very diverse, and findings involving both the central nervous system and the peripheral nervous system have been observed. Although mild symptoms such as dizziness, headache, and smell-taste disorders are frequently observed, there may also be findings that suggest a poor prognosis, such as impaired consciousness, acute cerebrovascular disease, and seizure[4]. It is thought that the neurotropic effects of SARS-CoV-2 can manifest in the following ways: Figure 1. (1) the direct invasion of coronavirus into the nervous system, (2) damage of the nervous system secondary to inflammation in the body, (3) hypoxia due to respiratory and cardiac system involvement, and (4) changes in coagulation parameters related to infection and inflammation[5]. The inflammatory response is an important process that indicates the progression of the infection. Circulating cells, which are biochemical parameters that reflect inflammation and immune response, are potential predictors of patient prognosis[6]. Many hematological abnormalities have been detected in coronavirus disease 2019 (COVID-19) patients, such as lymphopenia, eosinopenia, neutrophilia, thrombocytopenia, and changes in the neutrophil-to-lymphocyte ratio. These hematological parameters have also been an important guide for predicting overall prognosis, response to treatment, and mortality[6–8]. Some hematological abnormalities have also been associated with neurological conditions, such as headache, ischemic cerebrovascular events, and neuropathies. Other forms of system involvement in COVID-19 infection also affect the response and progression of the disease[9].

We know that neurological symptoms can manifest in COVID-19 and can adversely affect clinical outcomes. If we can predict the presence of neurological symptoms with simple methods, we can greatly contribute to obtaining an accurate prognosis.

In this study, we aimed to compare neurological involvement in COVID-19 patients with laboratory findings and evaluate the predictive value of these low-cost, practical tests.

MATERIALS AND METHODS

Study population

Our study includes patients admitted to the Emergency Department of Pamukkale University Medical Faculty with the suspicion of COVID-19 who were hospitalized and discharged from the Chest Disease, Infectious Disease, Clinical Microbiology, or Internal Medicine Departments or followed-up at home between March 13 and June 2, 2020. We excluded severe cases in which the patients could not answer our questions and were treated in the intensive care unit. Phone numbers were obtained from the primary physicians of 170 patients. All patients had been diagnosed with COVID-19 through RT-PCR of swab samples taken from the nasopharynx, and laboratory tests were performed. One hundred and three patients who met the study criteria could be reached; they were asked about their demographical information, initial symptoms, comorbidities, and neurological findings by two experienced neurologists.

Neurological examination

We classified patients into 3 groups based on neurological symptoms. The first group had symptoms related to the central nervous system (CNS), such as headache, dizziness, acute cerebrovascular disease, seizure, and ataxia. The second group had symptoms involving the peripheral nervous system (PNS), such as smell, taste, vision impairment, facial paralysis, and neuropathy. The last group experienced sleep disturbances (increased sleep time or insomnia) and myalgia.

Laboratory measurements

We recorded the patients' and controls' clinical

information and laboratory findings, which were obtained from the hospital software with the consent of the hospital and participants. In addition, because of the infectiousness of hospitals, verbal consent was obtained from the participants before the interview. In the same period, the control group consisted of 103 patients who presented to the emergency department with complaints of conditions other than acute infection whose RT-PCR COVID-19 tests were negative and who had no history of chronic disease, COVID-19 infection, or drug use. They were matched to the patient group by age and gender (Figure 1).

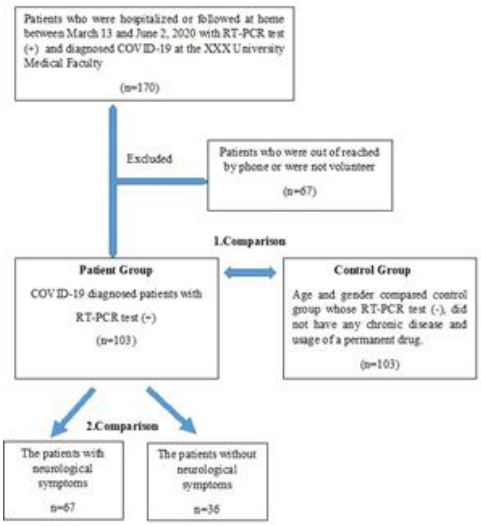

Figure 1. Design of the study

The complete blood count (CBC) analysis was carried out using a Mindray BC6800 hematology analyzer system (Mindray Corp, Shenzhen, China) through the electrical impedance and light scattering method. We calculated monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) from laboratory findings.

For the CBC, involving neutrophil, monocyte, lymphocyte, and platelet counts, we analyzed 22 parameters, which we used to calculate the ratios in our hematology laboratory. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Pamukkale University (#60116787-020/34130).

Statistical analysis

All statistical analyses were performed using SPSS 25.0 software. Kolmogorov–Smirnov and Shapiro–Wilk testswere used fordeterminationof normal distribution. Continuous variables were defined in terms of mean ± standard deviation and median (minimum–maximum values), and categorical variables were defined by number and percent. For independent group comparisons, we used the independent samples t test when parametric test assumptions were provided and the Mann–Whitney U test when parametric test assumptions were not provided ((The tests used for the examined variables are expressed as "a – Mann Whitney U test" and "c – Independent samples t test" in our tables). Differences. Differences between categorical variables were evaluated using the chi-square test. Logistic regression analysis models were used to determine the risk factors. A p-value< 0.05 was considered statistically significant.

RESULTS

One hundred and three RT-PCR diagnosed COVID-19 patients for whom we were able to obtain hematological parameters were included in the study; 103 age and gender-matched controls with negative RT-PCR tests and no history of chronic disease or drug usewere also included. The patients' mean age was 42 ± 17 years, and the controls' mean age was 38 ± 13 years. Sixty (58.3%) of patients were male, and 43 (41.7%) were female. The demographical and clinical findings are shown in Table 1.

Fifty-five (53.4%) patients had at least one comorbidity. Among those comorbidities, 15.5% had respiratory system disease, 12.6% had diabetes mellitus (DM), 10.7% had hypertension (HT), 10.7% had heart disease, 5.8% had a malignancy, and 30.1% had some other disease (thyroid, psychiatric, etc.). At least one admission symptom was present in 85 (82.5%) of the patients who were followed; the other 18 (17.5%) were asymptomatic. Thirty-three (32%) patients were healthcare professionals. Forty-three (41.7%) patients had chest computed tomography (CT) image findings supporting COVID-19.

The most common initial symptoms were cough (66%), sore throat (55.3%), fever (42.7%), dyspnea (%29.1), diarrhea (7.8%), and stomachache (6.8%). Sixty-seven patients (65%) had at least one neurological symptom in this disease process. There were no significant differences between patients with and without neurological symptoms in terms of age,

gender, and having comorbidities. However, CNS findings were more common in females than in males (p=0.01).

Table 1. Demographic - clinical findings and comorbidities of population

Characteristics	Patients (n=103)		Controls (n=103)	P value
Age,Mean±SD,y	42.46 ± 16.92		37.94 ± 12.55	0.092 [a]
Sex				
Female (%)	43 (41.7%)		54 (52.4%)	0.125 [b]
Male (%)	60 (58.3%)		49 (47.6%)	
	+ (%)	- (%)		
Healthcareproffesionals	33 (32%)	70 (68%)		
Smoking	30 (29.1%)	73 (70.9%)		
Comorbidities	55 (53.4%)	48 (46.6%)		
Respiratuar system disease	16 (15.5%)	87 (84.5%)		
Diabetes Mellitus	13 (12.6%)	90 (87.4%)		
Hypertension	11 (10.7%)	92 (89.3%)		
Cardiac Disease	11 (10.7%)	92 (89.3%)		
Malignancy	6 (5.8%)	97 (94.2%)		
Others	31 (30.1%)	48 (46.6%)		
Neurological symptoms	67 (65%)	36 (35%)		
CNS	55 (53.4%)	48 (46.6%)		
Headache	48 (46.6%)	55 (53.4%)		
Dizziness	19 (18.4%)	84 (81.6%)		
Ataxia	6 (5.8%)	97 (94.2%)		
Impaired consciousness	4 (3.9%)	99 (96.1%)		
Seizure	1 (1%)	102 (99%)		
PNS	42 (40.8%)	61 (59.2%)		
Smell impairment	32 (31.1%)	71 (68.9%)		
Taste impairment	28 (27.2%)	75 (72.8%)		
Neuropathic pain	11 (10.7%)	92 (89.3%)		
Vision changes	3 (2.9%)	100 (97.1%)		
OSS	67 (65%)	36 (35%)		
Myalgia	47 (45.6%)	56 (54.4%)		
Sleep disturbances	47 (45.6%)	56 (54.4%)		
-Increased sleep time	23 (22.3%)	80 (77.7%)		
-Decreased sleep time	24 (23.3%)	79 (76.7%)		
Positive Chest CT findings	43 (41.7%)	60 (58.3%)		

CNS, central nervous system; PNS, peripheral nervous system; OSS, Other system symptoms; CT, Computed tomography
+: Healthcareproffesionals, smoking, comorbidities and neurological symptoms positive
-: Healthcareproffesionals, smoking, comorbidities and neurological symptoms negative
a: Mann Whitney U test; b: Chi Square test

Fifty-five patients (53.4%) had CNS symptoms, 42 (40.8%) had PNS symptoms, and 67 patients (65%) had other symptoms, including sleep disturbances and myalgia. The most common neurological symptom was headache (46.6%); others were smell impairment (31.1%), taste impairment (27.2%), dizziness (18.4%), neuropathic pain (10.7%), ataxia (5.8%), impaired consciousness (3.9%), and vision impairment (2.9%). Sleep disturbance was found in 47 patients (23 had increased daily sleep time, and 24

patients had difficulty either getting to sleep), and myalgia was found in 47 (45.6%) patients. There were some differences in hematological parameters between the patient and control groups (Table 2). The patient group had lower white blood cell (7.46 vs. 8.49 x 10^9/L, p=0.004), neutrophil (4.27 vs. 5.01 x 10^9/L, p=0.02), lymphocyte (1.99 vs. 2.44 x 10^9/L, p=0.001), eosinophil (0.08 vs. 0.14 x 10^9/L, p=0.001), basophil (0.02 vs. 0.03 x 10^9/L, p=0.005), and platelet (244 vs. 254 x10^9/L, p=0.05) counts and higher average monocyte-to-lymphocyte ratio (MLR) (0.22 vs. 0.20, p=0.02) and platelet-to-lymphocyte ratio (PLR) (0.12 vs. 0.10, p=0.01). There were not any significant differences in terms of age, gender, or the other hematological parameters between the patient group and the control group (p>0.05).

We compared the hematological parameters of patients with neurological symptoms and those of patients without neurological symptoms (Table 3).

Table 2. Laboratory findings of all population

	Control (n=103)		Patient (n=103)		
	Mean ± S.D.	Med (min - max)	Mean ± S.D.	Med (min - max)	P value
WBC (10^9/L)	8.95± 2.93	8.49(2.93 – 4.07)	7.99 ± 3.29	7.46 (3.298 – 3.14)	0.004*[a]
Neutrophil (10^9/L)	5.61± 2.66	5.01(2.66 – 1.36)	5.07± 2.77	4.27(2.77 – 1.20)	0.026*[a]
Lymphocyte (10^9/L)	2.58± 0.83	2.44(0.83- 0.93)	2.20± 1.05	1.99(1.05- 0.50)	0.001*[a]
Monocyte (10^9/L)	0.55 ± 0.23	0.50 (0.23 – 0.25)	0.53 ± 0.24	0.49 (0.24 – 0.11)	0.583 [a]
Basophil (10^9/L)	0.003± 0.001	0.003 (0.001 – 0.001)	0.002± 0.001	0.002 (0.001- 0)	0.005*[a]
Eosinophil (10^9/L)	0.016± 0.012	0.014 (0.012- 0)	0.01 ± 0.02	0.008 (0.023- 0)	0.001*[a]
RBC (10^9/L)	4.95 ± 0.56	4.92 (0.56 – 3.8)	4.95 ± 0.61	4.92 (0.61 – 3.27)	0.981 [c]
Hb (g/L)	14.27 ± 1.79	14.5 (1.79 – 10.6)	14.25 ± 1.71	14.4 (1.71- 10)	0.911 [c]
Hct (%)	42.48 ± 4.57	43.2 (4.57 – 33.2)	42.13 ± 4.45	42.2 (4.45 – 30.8)	0.711 [c]
RDW (%)	13.59 ± 1.29	13.3 (1.29 – 11.7)	13.68 ± 1.36	13.2 (1.36 – 11.8)	0.594 [c]
PLT (10^9/L)	261.73 ± 60.54	254 (60.54- 96)	243.76 ± 69.79	244 (69.79- 66)	0.05*[c]
MPV (fL)	9.56 ± 1.09	9.4 (1.09 – 7.5)	9.51 ± 1.06	9.6 (1.06 – 6.8)	0.771 [c]
MLR	0.24 ± 0.15	0.2 (0.15 – 0.1)	0.3 ± 0.22	0.22 (0.22 – 0.08)	0.022*[a]
NLR	2.47 ± 1.86	1.88 (1.86 – 0.49)	2.96 ± 2.62	2.06 (2.62 – 0.59)	0.304 [a]
PLR	0.11 ± 0.04	0.1 (0,04- 0,03)	0.13 ± 0.06	0.12 (0.06 – 0.02)	0.014*[a]

WBC, White blood cell; RBC, Red blood cell; Hb, Hemoglobin; Hct, Hematocrit; RDW, Red cell distribution width; PLT, Platelet; MPV, Mean platelet volume; MLR; Monocyte to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio
* $p < 0.05$; statistically significant; a: Mann Whitney U test; c: Independent samples t test

There were no significant differences in any hematological parameters between the patients with neurological symptoms and those without neurological symptoms (p>0.05). However, in the CNS group (consisting of patients who experienced headache, dizziness, acute cerebrovascular disease, seizure, and ataxia), red blood cell (RBC) (4.82 vs. 5.13 x 10^9/L, p=0.03) and hematocrit (41.5% vs. 42.8%, p=0.03) counts were lower. In the PNS group (consisting of patients who experienced smell, taste and/or vision impairment, facial paralysis, and neuropathy) lymphocyte (1.82 vs. 2.19 x10 /L, p=0.02) and platelet counts (229.5 vs. 256 x10^9/L, p=0.02) were lower. In addition, eosinophil counts were statistically significantly lower in patients with sleep disturbances and muscle pain than in those without (60 vs. 120 x 10^9/L, p=0.01) (Table 4).

Table 3. Hematological parameters according to having neurological symptoms

Neurological Symptoms	+ (n=67)		- (n=36)		
	Mean ± S.D.	Med (min - max)	Mean ± S.D.	Med (min - max)	P value
Age	40.78± 17.09	37 (16- 99)	45.58± 16.38	44.5 (14- 79)	0.077 [a]
WBC	8.03 ± 3.55	7.46(3.29 –20.1)	7.93 ± 2.79	7.58(3.14- 15.56)	0.696 [a]
Neutrophil (10^9/L)	5.05± 3.00	4.27(1.20 – 16.3)	5.11 ± 2.32	4.28(1.480 – 12.51)	0.594 [a]
Lymphocyte (10^9/L)	2.26± 1.13	2.07(0.50 – 5.72)	2.08± 0.88	1.91(0.74 – 3.91)	0.571 [a]
Monocyte(109/L)	0.54± 0.26	0.49 (0.11- 1.73)	0.52 ± 0.21	0.53 (0.25 – 1.20)	0.096 [a]
Basophil (10^9/L)	0.02 ± 0.01	0.02(0 – 0.07)	0.02± 0.01	0.025 (0.01 – 0.06)	0.070 [a]
Eosinophil (10^9/L)	0.14 ± 0.17	0.09(0 – 0.71)	0.17± 0.32	0.08 (0.01 – 1.81)	0.978 [a]
RBC (109/L)	4.89 ± 0.59	4.82 (3.27 – 6.43)	5.06 ± 0.65	5.07 (3.43 – 6.16)	0.188 [c]
Hb (g/L)	14.09 ± 1.65	14.3 (10 – 17.2)	14.53 ± 1.81	14.55 (10.8 – 17.6)	0.214 [c]
Hct (%)	41.66 ± 4.37	42.2 (30.8 – 51.4)	43.01 ± 4.54	42.75 (31.1 – 52.3)	0.141 [c]
RDW (%)	13.66 ± 1.38	13.4 (11.8 – 20.4)	13.71 ± 1.33	13.2 (12.2 – 17.3)	0.747 [a]
PLT (10^9/L)	239.96 ± 62.26	235 (66- 370)	250.83 ± 82.5	246 (123- 511)	0.879 [a]
MPV (fL)	9.55 ± 1.02	9.7 (6.8 – 11.7)	9.45 ± 1.15	9.35 (7.4 – 11.7)	0.667 [c]
MLR	0.3 ± 0.24	0.21 (0.08 – 1.33)	0.29 ± 0.16	0.24 (0.14 – 0.86)	0.408 [a]
NLR	2.99 ± 2.89	1.95 (0.59 – 14.69)	2.9 ± 2.05	2.25 (1.01 – 11.85)	0.233 [a]
PLR	0.13 ± 0.07	0.11 (0.02 – 0.38)	0.13 ± 0.05	0.13 (0.07 – 0.31)	0.33 [a]

WBC, White blood cell; RBC, Red blood cell; Hb, Hemoglobin; Hct, Hematocrit; RDW, Red cell distribution width; PLT, Platelet; MPV, Mean platelet volume; MLR; Monocyte to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio
+: Neurological symptoms positive; - Neurological symptoms negative
* $p < 0.05$ statistically significant; a: Mann Whitney U test; c: Independent samples t test

Table 4. The significant hematological findings in classified neurological symptoms

CNS	+ (n=55)		- (n=48)		
	Mean ± S.D.	Med (min - max)	Mean ± S.D.	Med (min - max)	P value
RBC	4.83±0.57	4.82 (3.27 – 6.25)	5.09 ± 0.64	5.13 (3.43 – 6.43)	0.033* [c]
Hct	41.28±4.57	41.5 (30.8 – 51.4)	43.1 ± 4.15	42.8 (31.1 – 52.3)	0.038* [c]
PNS		+ (n=42)		- (n=61)	
Lymphocyte	1.97±1.14	1.82 (0.5 – 5.72)	2.35±0.96	2.19 (0.74 – 5.5)	0.025* [a]
PLT	225.26 ± 62.28	229.5 (66- 336)	256.49 ± 72.29	256 (123- 511)	0.025* [c]
OSS		+ (n=67)		- (n=36)	
Eosinophil	0.12 ± 0.17	0.06(0- 0.71)	0.21 ± 0.32	0.12 (0.01 – 0.18)	0.013* a

RBC, Red blood cell; Hct, Hematocrit; PLT, Platelet; CNS, Central nervous system; PNS, Peripheral nervous system; OSS, Other System Symptoms (Myalgia and sleep disturbances); +: Nervous system findings positive; -: Nervous system findings negative
* $p < 0.05$ statistically significant; a: Mann Whitney U test; c: Independent samples t test

In the evaluation with univariate logistic regression analysis for the effects of factors on the presence of neurological symptoms, the presence of muscle pain increases the risk of the presence of neurological symptoms by 3.2 times (Odds ratio=3.2, p =0.009). In this way, sleep disorders (Odds ratio = 2.583, p = 0.002), taste changes (Odds ratio = 3.618, p = 0.009), neuropathic pain (Odds ratio = 10.444, p = 0.028)

and muscle pain (Odds ratio = 2.583, p = 0.002) in particular have been shown to indicate risk of CNS findings. In addition, the patients with PNS findings exhibited more respiratory system findings, which were shown via standard CT images (odds ratio=2.947, p=0.009).

DISCUSSION

We compared our patients in 2 ways, patients vs. controls and patients with neurological symptoms vs. those without neurological symptoms, whereas previous studies compared severe and non-severe cases according to clinical status. Some important hematological findings appeared. White blood cell, neutrophil, lymphocyte, eosinophil, basophil, and platelet counts were lower and monocyte-to-lymphocyte ratios and platelet-to-lymphocyte ratios were higher in patients than in controls. In the group with central nervous system findings, red blood cell and hematocrit counts were lower than in other groups; in the group with peripheral nervous system findings, lymphocyte and platelet counts were lower than in other groups; and in the group with sleep disturbances and muscle pain, eosinophil counts were lower than in other groups.

The nervous system injury caused by SARS-CoV-2 is related to several pathways, including direct infection pathways (blood circulation pathways and neuronal pathways), hypoxia, angiotensin converting enzyme 2 (ACE2), immune injury, and other mechanisms[10]. In these ways, SARS-CoV-2 infection can evolve into permanent damage that can lead to neurological diseases in line with host immune mechanisms. Immunity plays an important role in the neurological symptoms of COVID-19.

In our study, the patients' initial WBC, neutrophil, lymphocyte, eosinophil, basophil, and platelet counts were lower than the controls'. Altunisik et al. found a lower lymphocyte count in COVID-19 patients with severe neurological symptoms. Altunisik et al. also revealed that the nervous system and skeletal muscle system may be among the viral targets. Some of their laboratory findings are similar to those of our study, such as lower lymphocyte count. But against to our study higher neutrophil counts related with neurological symptoms in infected patients with SARS-CoV-210. And similar findings, like lower lymphocyte count and higher neutrophil counts in severe COVID-19 patients than in recovered patients, were found by Ferrari et al[11]. Sun et al. found lower lymphocyte and WBC counts in COVID-19 patients than in controls, as in our study. They mention that these blood abnormalities were related to the severity of the disease[12].

We do not have much data regarding the relationship between neurological involvement and hematological findings in COVID-19. However, hematological abnormalities due to COVID-19 were explained as following mechanisms, supporting our study. The distribution of the ACE receptor defined for the function of SARS-CoV-2 shows us the rationale for the neurological involvement[4]. After SARS-CoV-2 enters the cell and binds to the ACE2 receptor, macrophages are activated, releasing chemokines and inducing factors, and tissue damage occurs because of excessive mononuclear cell infiltration. It is thought that the number of lymphocytes and monocytes decreases due to this condition[3,11]. An autopsy performed in a histopathological study of a 3-case COVID-19 series showed that CD4 and CD8 mediated a decrease in T lymphocyte counts in the spleen and lymph nodes, and the process of myelopoiesis in the bone marrow was compromised. It is known that the low platelet count in COVID-19 patients is due to the prothrombotic effect of SARS-CoV-2 and is associated with increased platelet consumption secondary to thrombosis in the lungs and other organs and decreased platelet production[12]. In addition, eosinophils migrate to the infected area to fight viruses in the acute phase of infection, and the number of eosinophils in peripheral blood decreases[13]. Lu et al. showed that low eosinophil counts are a sensitive marker for COVID-19 prognosis[14].

We did not find any differences in any hematological parameters between the patients who had neurological symptoms and those who did not have neurological symptoms. However, we observed that some clinical signs, such as muscle pain, increased the risk of neurological findings. Vacchiano et al. also discovered an association between muscle pain and a neurological symptom (headache)[15]. We found that sleep disturbances, taste disorders, neuropathic pain, and muscle pain also increased the risk of CNS findings, and thorax CT findings related to COVID-19 increased the risk of PNS symptoms.

In our study, patients with CNS findings had lower RBC and hematocrit values, whereas patients with PNS findings had lower leukocyte and platelet values. Furthermore, we found that in patients with muscle pain and sleep disorders, eosinophil counts were

lower. This clinically shows us the risk of CNS findings in patients with low erythrocyte and hematocrit values, the risk of PNS findings in patients with low PLT and leukocyte levels, and the risk of muscle pain and sleep disturbance in patients with low eosinophil values.

There was no significant difference in NLR between patients and controls in our study. NLR was shown to be an independent prognostic biomarker for the severity of COVID-19 in recent studies. Yang et al. showed a statistically significant difference in NLR between severe and non-severe patients[11]. Our patients were non-severe patients we could reach by phone who recovered and were discharged from the hospital. In addition, our control group was selected meticulously; even those with a history of chronic illness and chronic drug use were excluded from the control group. In addition, in Yang's study, the severe patients were generally older than the non-severe patients, but in our population, the controls' and patients' ages were similar. However, the MLR and PLR of our patients were significantly higher than those of our control group, as Sun et al. found[13].

In our study, 65% of the patient population had at least one neurological symptom. Mao et al. showed that neurological symptoms were present in approximately 36.4% of COVID-19 cases, in addition to systemic and respiratory symptoms[4]. Consistent with previous studies, various neurological manifestations were seen in our patient population, and symptoms involving the CNS were more common than those involving the PNS. Headache was the most common neurological symptom in our study, whereas dizziness and taste disorders were among the most common symptoms in other studies[4,15]. The headaches experienced by COVID-19 patients are often tension headaches, as Vacchiano et al. showed[15]. This symptom was followed by PNS findings, such as smell (31.1%) and taste changes (27.2%), in our study. In addition to these, we found that 45.6% of the patient population had sleep disturbances.

Our study has some limitations. First, it was a one-center, retrospective study. Second, the laboratory findings were obtained only on the patient presented to the hospital; we could not follow-up on these hematological parameters. Third, our study population consisted of patients who had clinically improved, so our results reflect a healthier population, and we could not inquire about the symptoms of patients in more severe clinical situations. Fourth, we identified the symptoms from the patients' subjective reports. Finally, because of the outbreak period, advanced neuroimaging (such as magnetic resonance imaging) and diagnostic procedures (such as lumbar puncture and electromyography) were avoided to reduce the risk of cross-infection.

In conclusion, we have revealed some hematological abnormalities in COVID-19 patients. Therefore, we should consider the possibility of developing neurological symptoms in COVID-19 patients with low cell counts and in those with certain symptoms, such as muscle pain. However, new studies with larger patient populations and with follow-up periods are needed to further elaborate these findings.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ÇE, ST, EA, ZU; Veri toplama: SD, EU, İHA; Veri analizi ve yorumlama: ST, ZU, EA; Yazı taslağı: ST, ÇE, ZU; İçeriğin eleştirel incelenmesi: HA, ÇE; Son onay ve sorumluluk: ST, ZÜ, ÇE, EA, TS, SD, HA, EU, MS, İHA; Teknik ve malzeme desteği: TS, SD, EU, İHA; Süpervizyon: ÇE, HA, TS; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Pamukkale Üniversitesi Girişimsel Olmayan Klinik Arnaştırmalar Etik Kurulundan 10.06.2020 tarih ve 11 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Yazarın Notu: COVID-19 pandemisinde tüm gücüyle çalışan tüm sağlık çalışanlarımıza teşekkür ederiz.

Author Contributions: Concept/Design : ÇE, ST, EA, ZU; Data acquisition: SD, EU, İHA; Data analysis and interpretation: ST, ZU, EA; Drafting manuscript: ST, ÇE, ZU; Critical revision of manuscript: HA, ÇE; Final approval and accountability: ST, ZÜ, ÇE, EA, TS, SD, HA, EU, MS, İHA; Technical or material support: TS, SD, EU, İHA; Supervision: ÇE, HA, TS; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee by its decision dated 10.06.2020 and numbered 11.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support
Acknowledgement: We would like to thank all our healthcare professionals who have been working with all their might in the COVID-19 pandemic.

REFERENCES

1. Hasöksüz M, Kiliç S, Saraç F. Coronaviruses and sars-cov-2. Turk J Med Sci. 2020;50:549-56.
2. Bostan S, Erdem R, Öztürk YE, Kılıç T, Yılmaz A. The effect of COVID-19 pandemic on the Turkish society. Electron J Gen Med. 2020;17:1-8.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683-90.
5. Acar T, Demirel EA, Afşar N, Akçal A, Demir GA, Alagöz AN et al. The COVID-19 from neurological

overview. Turk Noroloji Derg. 2020;26:58-108.
6. Yang A, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int immunopharmacol. 2020;84:106504.
7. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chem Lab Med. 2020;58:1021-8.
8. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
9. Extance A. Covid-19 and long term conditions: what if you have cancer, diabetes, or chronic kidney disease? BMJ. 2020;368:1-2.
10. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22.
11. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420-22.
12. Salamanna F, Maglio M, Landini MP, Fini M. Platelet functions and activities as potential hematologic parameters related to Coronavirus Disease 2019 (Covid-19). Platelets. 2020;31:627-32.
13. 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;507:174-80.
14. Lu G, Wang J. Dynamic changes in routine blood parameters of a severe COVID-19 case. Clin Chim Acta. 2020;508:98–102.
15. Vacchiano V, Riguzzi P, Volpi L, Tappatà M, Avoni P, Rizzo G et al. Early neurological manifestations of hospitalized COVID-19 patients. Neurol Sci. 2020;41:2029–31.