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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

RELATIONSHIP BETWEEN CLINICAL AND PCR-CT VALUE IN COVID-19 PCR POSITIVE STROKES

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ABSTRACT

INTRODUCTION: By comparing the demographic characteristics, blood parameters and radiological images of patients with cerebrovascular disease (CVD) who were positive for COVID-19 by PCR (Polymerase Chain Reaction) and diagnosed with CVD and COVID-19 PCR-negative patients who had CVD in the same period, COVID-19 and It is aimed to explain the relationship between CVD and to show the relationship between viral load and CVD clinic.
METHODS: 20 patients who had CVD while being positive for COVID-19 PCR, and patients with similar age and gender who had CVD during the same period as the control group, were included in the study. Demographic characteristics diseases, brain Computed Tomography (CT) and brain Diffusion Magnetic Resonance Imaging (MRI) stroke topography and vascular irrigation areas involved, blood parameters such as white blood cell (WBC), neutrophil and lymphocyte ratio (NLR), C-reactive protein (CRP), D-dimer, fibrinogen, ferritin, international normalization ratio (INR), activated partial thromboplastin time (aPTT) values were examined and compared between groups. COVID -19 Reporting and Data System (CO-RADS) was evaluated with thorax CT in PCR+ patients. Neurological status was evaluated with the National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Modified Rankin Scale (mRS), and compared with NLR, CRP, PCR-CT (cycle threshold) and CO-RADS.
RESULTS: There was no statistical difference between the groups in terms of ischemic stroke risk factors such as Hypertension (HT), Diabetes Mellitus (DM), Atrial Fibrillation (AF). NLR, CRP and ferritin were found to be statistically significantly higher in COVID-19 PCR positive patients. No correlation was found between NLR, PCR-CT value and stroke severity.
DISCUSSION AND CONCLUSION: There is no relationship between NLR, CRP, PCR-CT values and neurological clinics in patients who have co-existing CVD with COVID-19.
Keywords: COVID-19, stroke, PCR-Ct, neutrophil lymphocyte ratio, NIHSS.

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COVID-19 PCR POZİTİF İNMELERDE KLİNİK VE PCR-CT DEĞERİ ARASINDAKİ İLİŞKİ

ÖZ

GİRİŞ ve AMAÇ: COVID-19, PCR (Polymerase Chain Reaction) ile pozitif gösterilmiş ve serebrovasküler hastalık (SVH) tanısı alan hastalarla, COVID-19 PCR negatif olan aynı dönem SVH geçiren hastaların demografik özellikleri, kan parametreleri ve radyolojik görüntüler açısından karşılaştırarak COVID-19 ve SVH arasındaki ilişkinin açıklanması ve viral yük ile SVH kliniği arasındaki ilişkinin gösterilmesi hedeflenmiştir.

YÖNTEM ve GEREÇLER: COVID-19 PCR pozitif iken SVH geçiren 20 hasta ile kontrol grubu olarak aynı dönem SVH geçirmiş benzer yaş ve cinsiyette COVID-19 PCR negatif hastalar çalışmaya dahil edilmiştir. Demografik özellikler hastalıklar, beyin Bilgisayarlı Tomografi (BT) ve beyin Difüzyon Magnetik Rezonans Görüntüleme (MRG) inme topografisi ve tutulan vasküler sulama alanları, kan parametrelerinden beyaz küre (BK), nötrofil ve lenfosit oranı (NLR), C-reaktif protein (CRP), D-dimer, fibrinojen, ferritin, uluslararası normalizasyon oranı (INR), aktive parsiyel tromboplastin zamanı (aPTT) değerleri incelenmiş ve gruplar arasında karşılaştırılmıştır. PCR+ hastalarda Toraks BT ile CORADS bakılmıştır. National Institutes of Health Stroke Scale (NIHSS), Glaskow Koma Skalası (GKS), Modifiye Rankin Skalası (mRS) ile nörolojik durumlarına bakılmış, NLR, CRP, PCR-CT (cycle threshold) ve CORADS ile kıyaslanmıştır.

BULGULAR: Gruplar arasında Hipertansiyon (HT), Diyabetes Mellitus (DM), Atriyal Fibrilasyon (AF) gibi iskemik inme risk faktörleri açısından istatistiksel olarak fark görülmemiştir. COVID-19 PCR pozitif olanlarda NLR, CRP ve ferritin istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur. NLR, PCR-CT değeri ile inme şiddeti arasında korelasyon saptanmamıştır.

TARTIŞMA ve SONUÇ: COVID-19 ile eş zamanlı SVH geçiren hastalarda NLR, CRP, PCR-CT değeri ile nörolojik klinik arasında ilişki yoktur.

Anahtar Sözcükler: COVID-19, inme, PCR-Ct, nötrofil lenfosit oranı, NIHSS.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been posed a serious public health threat around the world, leaving millions of people at risk. (1). COVID-19 not only affected the respiratory system but also caused various neurological symptoms. In addition to common neurological symptoms such as taste and smell disorders, myalgia, headache, brain fog, mental changes, and dizziness, alarming neurological symptoms and complications such as stroke, cerebral vein thrombosis, epileptic seizures, meningoencephalitis, Guillain-Barré syndrome, Miller Fisher syndrome, acute myelitis and posterior reversible encephalopathy syndrome (PRES) have also been observed (2).

In the meta-analysis by Favas et al., it was reported that acute ischemic stroke incidence among COVID-19 patients was 2.3% and the prevalence of acute cerebrovascular disease was 2.6% (3). In hospitalized COVID-19 patients with severe infection, acute cerebrovascular disease prevalence reaches almost 6% (4). In a study carried out in Turkey, a history of stroke was found in 1.4% of COVID-19 patients (5).

While it is believed that viral infections activate and initiate a coagulation cascade, cross-reactivity occurs between haemostasis and inflammation. COVID-19 causes sepsis-induced coagulopathy, characterized by increased prothrombin time, elevated D-Dimer levels, and thrombocytopenia without hypofibrinogenemia (6). Hypercoagulation causes increased arterial and venous occlusions. There is evidence that COVID-19 patients have strokes secondary to more severe anterior circulation large vessel occlusion, with a higher rate of multivessel occlusion and higher infarct core volume than control patients (7).

Today, the most accurate method of diagnosis for COVID-19 is the detection of the genetic material of the disease-causing virus by real-time reverse transcription polymerase-chain reaction (RT-PCR) in respiratory tract samples (8). Various numbers of different gene regions are used in different test kits, and RT-PCR protocols appropriate to these gene regions are applied. As target regions, S (spike) and N (nucleocapsid) genes and non-structural RdRp and ORF1a/b genes are frequently preserved in the evolutionary process and are widely used in diagnosis since they have the least cross-reactivity (9). The cycle number at which the fluorescence generated within a reaction crosses the fluorescence threshold, a fluorescent signal significantly above the background fluorescence is called the

threshold cycle value (threshold cycle=Ct). Ct value is the time when the system begins to notice the increase in the fluorescence and the PCR product begins to increase exponentially in the log-linear phase, allowing us to evaluate the viral load semiquantitative (10). As the Ct value increases, the viral load decreases. A study conducted in China found that COVID-19-positive severe cases had higher viral load and longer virus persistence (11). In a previous study on Ct values in MERS-Cov, also a respiratory tract infection, lower Ct values were shown as the severity of the disease increased (10).

Our aim is to compare the clinical status of COVID-19 PCR-positive patients who had a stroke, and not vaccinated against COVID-19, and COVID-19 PCR-negative patients who had a stroke, and to show the relationship between the viral load and the clinical status in PCR-positive patients.

METHODS

Patient selection and study design: This study was started after the approval received from Aksaray University Human Research Ethics Committee (Date: 22.02.2021, No: 2021/01-58). The study was conducted retrospectively and in accordance with the Ethical Standards of the Helsinki Declaration. Patients who applied to Aksaray University Training and Research Hospital, who were diagnosed with stroke, had a COVID-19 PCR test, tested positive, and whose COVID-19 PCR-CT values were available, and randomly selected patients (selected without considering any parameters other than age and gender) of similar age and gender, diagnosed with stroke in the same period, COVID-19 PCR negative, and without COVID-19 symptoms were included in the study. Patient's detailed medical history was taken; their history of Hypertension (HT), Diabetes Mellitus (DM), and Atrial fibrillation (AF) was questioned, a neurological examination was performed, and during the first neurological examination, National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Modified Rankin Scale (mRS) were calculated, and neurological imaging was performed. Diffusion-weighted magnetic resonance imaging (MRI) and Brain Computed Tomography (CT)), coagulation parameters such as hemogram, electrolytes, international normalized ratio (INR), activated partial thromboplastin time (aPTT), D-dimer, fibrinogen, and C-reactive protein (CRP), ferritin values were studied. PCR-CT values of COVID-19 PCR-positive patients were accessed from the electronic hospital database. Carotid and vertebral color Doppler and echocardiography (ECHO) examinations were completed for each patient to investigate the stroke etiologies of patients. Patients who had a previous stroke, had neurological sequelae for different reasons, or had gait disorders before the stroke were not included in the study.

Evaluation methods: NIHSS, GCS, mRS scores, brain CT, and diffusion-weighted MRI examinations of the patients were evaluated by the neurologist. Thorax CT reports were reviewed. COVID-19 PCR and PCR CT values were evaluated by a microbiologist.

1-Demographic information form: The age and gender of the cases were recorded within the scope of their demographic characteristics. History of HT, DM, AF, and previous CVD were questioned within the scope of medical history.

2- Hemogram, biochemistry, coagulation, and acute phase reactants values: After CVD, hemogram, biochemistry, coagulation, and acute phase reactants were recorded. NLR was measured by dividing the number of neutrophils by the number of lymphocytes.

3- NIHSS: NIHSS is an 11-item neurological examination stroke scale used to evaluate neurological statuses such as consciousness, vision, sensation, movement, speech and language, and the items are scored between 0-4. As the score increases, neurological worsening increases.

4-Glasgow Coma Scale (GCS): It is a scale used to measure the level of consciousness by evaluating eye opening, verbal response, and motor response, with scores between 3 and 15. As the score increases, the patient's neurological condition improves.

5-mRS: It is a scale that determines stroke severity, the degree of disability or dependence, and is scored between 0-6. As the score increases, the patient's clinical status worsens.

6- SARS-CoV-2, RT-PCR test ve Ct values: Combined nasopharyngeal and oropharyngeal swab samples collected from the patients are sent to the laboratory in a viral transport medium (VTM). According to the manufacturer's instructions, viral nucleic acid extraction is performed from the samples. PCR testing is

performed by Bio-Rad CFX96 Touch (Bio-rad Laboratories, USA) device using the Bio-speedy SARSCov-2 (2019-nCoV) RT-qPCR Detection Kit (Bioeksen, Turkey) according to the manufacturer's instructions. With the kit studied, the N and ORF1ab gene regions of the SARSCoV-2 genome is targeted. The tests are evaluated according to the manufacturer's instructions, and the thermal cycle number (cycle threshold=Ct) values at which the fluorescent signal resulting from the amplification of the target genes reached the positivity threshold level are determined. It is interpreted as the lower the Ct value, the higher the viral RNA copy number.

7- COVID-19 reporting and information system (CO-RADS): In March 2020, the German Radiological Society developed a system, CO-RADS (COVID-19 Reporting and Data System) to indicate the suspicion of pulmonary involvement in thorax CT (negative/very low/low suspicious /uncertain, suspicious/typical) due to COVID-19 (12). In COVID-19 PCR-positive strokes, CO-RADS scores are examined according to the Thorax CT report.

Statistical analysis: The data were analyzed by SPSS Statistics 26.0 (Statistical Product and Service Solutions for Windows, Version 26.0, IBM Corp., Armonk, NY, U.S., 2019) package program. Continuous variables were presented as mean ± standard deviation (X±SD), median, and interquartile range values. Categorical variables are reported as numbers (n) and percentages (%). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. The groups were divided into two groups, positive and negative, according to the PCR test results. When parametric test assumptions were met, an independent sample t-test was used to compare independent group differences, and when parametric test assumptions were not met, the Mann-Whitney U Test was used. Since the normal distribution of data varies, Spearman correlation analysis was performed to assess the association between PCR-Ct and CO-RADS and GCS, NIHSS, mRS. $P<0.05$ was accepted as the significance level as a result of statistical tests.

RESULTS

The mean age of COVID-19 PCR-positive stroke patients was 76.7±9.35 years, and the mean age of COVID-19 PCR-negative stroke patients was 76.2±9.69 years (P=0.869). There were 12 (60%) female and 8 (40%) male patients in both groups. In the COVID-19-positive stroke group, large artery atherosclerosis was considered in 10 patients, small vessel disease in 4 patients, cardioembolic stroke in 4 patients, and cryptogenic stroke in 2 patients. In the COVID-19-negative stroke group, large artery atherosclerosis was considered in 9 patients, small vessel disease in 4 patients, cardioembolic stroke in 3 patients, and cryptogenic stroke in 4 patients. In Table 1, aPTT, leukocyte, fibrinogen, NLR, NIHSS mean, CRP, INR, ferritin, GCS, mRS median values of COVID-19 PCR-positive and COVID-19 PCR-negative strokes, PCR-positive and CO-RADS mean and D- dimer median values were indicated.

In PCR-positive patients GCS was 12.7±3.01, in PCR-negative patients, it was 13.5±3.08; although it was lower in PCR-positive patients, there was no significant difference. NIHSS was 8.35±5.71 in PCR-positive patients and 6.05±5.58 in PCR-negative patients. mRS was 3.55±1.78 in PCR-positive patients and 2.70±1.75 in PCR-negative patients. Although NIHSS and mRS PCR were higher in positive patients, no significant difference was found.

While HT was present in 13 patients in the COVID-19-positive group, it was present in 12 patients in the PCR-negative group. DM was present in 9 persons in both groups, and AF was present in 5 persons in both groups; there was no significant difference. In the PCR-positive group, right hemisphere involvement was 10 (50%), left hemisphere involvement was 8 (40%), and bilateral hemisphere involvement was 2 (10%). In the COVID-19 PCR-negative group, right hemisphere involvement was 9 (45%), left hemisphere involvement was 10 (50%), and bilateral involvement was 1 (5%). In the PCR-positive group, involvement of the anterior vascular system was 14 (70%), the posterior vascular system was 5 (25%), the anterior-posterior watershed zone was 1 (5%). In the COVID-19 PCR-negative group, involvement of the anterior vascular system was 11 (55%) and the posterior vascular system was 9 (45%). There was no difference in both groups in terms of hemisphere and vascular involvement.

As indicated in Table 2, no relationship was found between PCR-Ct value and CO-RADS, GCS, NIHSS, mRS. No relationship was found between

Table I. Comparison of blood parameters, clinical test scores according to PCR test and CO-RADS score in PCR-positive patients.

Variables	PCR (+) Mean±SS	PCR (-) Mean±SS	t	p
Aptt	28.66±5.38	26.89±2.95	1,285[a]	0.206
Wbc	8.98±3.38	9.21±4.19	-0.191[a]	0.850
NLO	11.24±10.73	3.95±2.78	2.939[a]	0.006*
Fibrinogen	506.50±114.20	393.40±101.12	1.978[a]	0.063
NIHSS	8.35±5.71	6.05±5.58	1.237[a]	0.224
CO-RADS	3.80±1.10			
	PCR (+)	PCR (-)	z	p
	Median (IQR)	Median (IQR)		
CRP	44.85 (84.45)	19.11 (46.26)	-3.489b	0.001*
INR	1.10 (0.06)	1.05 (0.19)	-1.489[b]	0.136
Ferritin	211.50 (281.10)	53.30 (242.25)	-3.119[b]	0.002*
D-dimer	2340(11767)			
GKS	14.00 (7.00)	15.00 (1.00)	-1.208[b]	0.227
MRS	4.50 (1.00)	3.00 (2.50)	-1.380[b]	0.168

PCR: Polymerase Chain Reaction, Mean: mean, SD: standard deviation, IQR: Interquartile range, Aptt: Activated partial thromboplastin time, INR: International Normalized Ratio, Wbc: Leukocyte, NLR: Neutrophil Lymphocyte Ratio, CRP: C-reactive protein , GCS: Glascow Coma Scale, NIHSS: National Institutes of Health Stroke Scale, CO-RADS: COVID-19 Reporting and Information System, MRS: Modified Rankin Scale, t: Independent sample t test score, z: Mann Whitney-U test score , a: Independent sample t test, b: Mann Whitney-U test, *: p<0.05

Table II. Relationship between PCR-Ct, CO-RADS and NLR and GCS, NIHSS, MRS clinical scores.

		PCR-Ct	NLO	CORADS	GKS	NIHSS	MRS
PCR-Ct	r						
	p	1.000					
NLO	r	0.120					
	p	0.624	1.000				
CORADS	r	0.169	0.220				
	p	0.488	0.350	1.000			
GKS	r	0.249	-0.309	0.163			
	p	0.304	0.052	0.492	1.000		
NIHSS	r	-0.323	0.309	-0.342	-0.825		
	p	0.223	0.063	0.179	0.001*	1.000	
MRS	r	-0.155	0.257	-0.327	-0.764	0.925	
	p	0.552	0.120	0.186	0.001*	0.001*	1.000

PCR-Ct: Polymerase Chain Reaction Cycle Threshold, NLR: Neutrophil Lymphocyte Ratio, CORADS: COVID-19 Reporting and Information System, GCS: Glasgow Coma Scale, NIHSS: National Institutes of Health Stroke Scale, MRS: Modified Rankin Scale, r: Spearman correlation coefficient, *: p<0.05.

CO-RADS and GCS, NIHSS, mRS. A negative correlation was detected between mRS and GCS, and a positive correlation was detected between mRS and NIHSS (P=0.001).

DISCUSSION AND CONCLUSION

COVID-19 PCR-positive stroke patients and COVID-19 PCR-negative stroke patients were compared, and NLR, CRP, and ferritin were found to be significantly higher in PCR-positive patients. No correlation was found between PCR-Ct, which shows the semi-quantitative virus load, and stroke clinic status. When we scanned the literature, we could not find a similar study looking at the relationship between PCR-Ct value and stroke clinic status.

In the study conducted by Bhatia et al., HT was observed in 42% of patients who had a stroke simultaneously with COVID-19, and DM was observed in 23.2% (13). In our patient group, these stroke risk factors were higher; HT was observed in 65% and DM was observed in 45%. This situation can be explained by the high prevalence of HT and DM in our society. In the study of Bhatia et al. anomaly and pathological findings were detected in the thorax CTs of COVID-19 PCR-positive patients (13); similarly, in our study, anomaly and pathological findings were seen in the thorax CTs of all COVID-19 PCR-positive patients.

With inflammation, the number of neutrophils increases, and the number of lymphocytes decreases. In pneumonia, NLR has been shown to be more sensitive than absolute lymphocyte or neutrophil count (14). In the study conducted by Torre et al., an increased NLR was observed in severe COVID-19 patients as compared to those with milder -moderate disease (15). In the meta-analysis carried out by Sarkar et al., mortality was evaluated with a total of 13.112

patients in 36 articles, and it was found that the risk of mortality was significantly increased in patients with high NLR at admission compared to the control group. Fifty-eight studies with a total of 12.986 patients were included to assess the severity of COVID-19, with critically ill patients being associated with higher baseline NLR (16). Increase in neutrophils and inflammatory markers, accompanied by a decrease in lymphocytes and an increase in NLR, was thought to indicate poor prognosis and severity of the disease (17). In our study, the existence of a relationship between neurological status and NLR in COVID-19 patients was evaluated, but no relationship was found.

CRP activates complement, induces the production of pro-inflammatory cytokines, and induces apoptosis, which can lead to serious consequences together with the inflammatory state during the disease (18).

In the COVID-19 pandemic, CRP is associated with tissue damage and poor prognosis. High CRP levels in the early stages of COVID-19 were associated with lung damage and disease severity (19). Ferritin, another acute phase reactant, was also found to be higher in critically ill patients (13). Higher NLR, C-reactive protein, and serum ferritin are associated with poor prognosis, while D-dimer and fibrinogen levels are associated with poor prognosis of stroke in COVID-19 (20). Although CRP and ferritin were detected to be higher in COVID-19 PCR-positive patients, their relationship with neurological status could not be determined.

Patients with high SARS-CoV-2 viral load showed lower Ct levels, which was associated with higher mortality in COVID-19 patients (n=875) in Brazil (21). Fajnzylber et al. reported that there is a relationship between plasma markers of inflammation and viral load from the respiratory tract. They reported that viral load can be considered a determinant of morbidity and mortality (22). Linear Ct values are inversely proportional to the number of signs and symptoms reported on the diagnostic swab; lower SARS-CoV-2 Ct values were independently associated with a higher number of signs and symptoms. Lower SARS-CoV-2 diagnostic Ct values were independently associated with a higher prevalence of 6-month sequelae among COVID-19 survivors (23). In the study conducted by Kurzeder et al., PCR-Ct value ≤26 was found to be a significant risk factor for mortality (24). There are also studies with different results. In the study conducted by Soeroto et al., no significant difference was found in the RT-PCR Ct value measured in the second week of the disease between the mild, moderate, severe, and critical groups (25). We could not find any study examining the relationship between clinical severity and PCR-Ct in patients who had a stroke during COVID-19. In our study, we wanted to show that there was an increase in neurological worsening with viral load, but we could not find a significant correlation.

Although lack of similar studies increases the value of our study, more meaningful results can be achieved if stroke clinic is evaluated with PCR-Ct value according to stroke etiologies in larger number of cases.

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Ethics

Ethics Committee Approval: The study was approved by Human Researches Ethics Committee of Aksaray University (Date: 22.02.2021, No: 2021/01-58).
Informed Consent: The author declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
Authorship Contributions: Surgical and Medical Practices: Dİ, ST. Concept: Dİ, ST. Design: Dİ, ST. Data Collection or Processing: Dİ, ST. Analysis or Interpretation: Dİ, ST. Literature Search: Dİ, ST. Writing: Dİ, ST.
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