Clinical and Experimental Health Sciences

Evaluation of D-Dimer and Neutrophil/Lymphocyte Ratios of COVID-19 Patients Whom Applied to Karapınar State Hospital

Saadet Kader[1], Turan Akdag[2], Levent Sariyildiz[3], Zeynep Ozel[4]

[1] Karapinar State Hospital, Biochemistry Laboratory, Konya, Türkiye.
[2] Necmettin Erbakan University, Meram Vocational School, Konya, Türkiye.
[3] Beyhekim Education and Research Hospital, Konya, Türkiye.
[4] Selcuk University, Selcuk University Faculty of Veterinary, Medicine, Department of Biostatistics, Konya, Türkiye.

Correspondence Author: Saadet Kader
E-mail: saadetkader@hotmail.com
Received: 27.11.2021 **Accepted:** 01.02.2022

ABSTRACT

Objective: The epidemic which caused by the SARS-CoV-2 virus were defined as COVID-19) and declared as a global pandemic by the World Health Organization (WHO) on March, 2020. Nowadays, many biochemical parameters related to the diagnosis and prognosis of COVID-19 are being investigated. Therefore, we aimed to evaluate D-dimer and neutrophil/lymphocyte ratios (NLR) of COVID-19 patients whom applied to Karapınar State Hospital.

Methods: Patients which consisted of 2523, whom diagnosed with COVID-19 between 11 March 2019 and 29 July 2021 at Karapınar State Hospital were included in the study. Age, gender and social history of the patients were recorded. From the results, the relationships between D-dimer and hemogram were evaluated.

Results: There was a high correlation between the variables HCT and HGB, PLT and PCT, NEUT# and WBC, and MCH and MCV (r=0.981, r=0.944, r=0.923, r=0.925). In addition, there was a high correlation between RBC and HCT and between RBC and HGB variables (r=0.852, r=0.795). There was a moderate correlation between WBC and MO#, MCHC and MCH, PDW and MPV (r=0.562, r=0.639, r=0.64). All the relationships between these variables were positive, and the value of the correlated parameter increases linearly by unit. Also, the highest positive relationships were between HCT and HGB, PLT and PCT, NEUT# and WBC, MCH and MCV. Moreover, D-dimer and NLR were not correlated (r= – 0.015, p=0.49).

Conclusion: In the study, no correlation was observed between D-dimer and neutrophil/lymphocyte ratios of COVID-19 patients. So, more comprehensive and further studies are needed to clarify these results.

Keywords: COVID-19, D-dimer, neutrophil/lymphocyte ratio

1. INTRODUCTION

On March 2020, the epidemic caused by the SARS-CoV-2 virus was declared as a global pandemic by the World Health Organization (WHO) (1). The virus was identified on January, 2020 as a new coronavirus that has not been detected in humans before. It was named as SARS-CoV-2 because of it's showing similarity to the causative SARS-CoV virus. SARS-CoV-2 virus is also thought to be transmitted from animals to humans by a zoonotic infection like SARS-CoV and MERS-CoV (2).

Compared to the non-COVID-19 infections, several studies reported significantly lower WBC or neutrophil counts in the early stages of the disease, although the mean WBC count does not exceed the lower limit to classify them as leukopenia or neutropenia (3). As conversely, leukocyte and neutrophil counts were found to be higher in severe groups with progression of COVID-19 disease, consistent with retrospective studies and other meta-analyses (4). These increase is a result of the susceptibility of secondary bacterial infections in severe COVID-19 (5). Lymphocytopenia is also observed in patients with positive COVID-19. The frequency of lymphopenia suggests that COVID-19 may have an effect on lymphocytes, especially T lymphocytes, including depletion of $CD4^+$ and $CD8^+$ cells, as did SARS-CoV (6, 7).

D-dimer composed of two D fragments of the fibrin, and formed by the activation of the plasmin enzyme. D-dimer display the activation of fibrinolysis and coagulation systems. Elevated D-dimer levels may be observed in physiological and pathological conditions such as surgery, cancer and inflammation (8). The increase in D-dimer value of infected patients is more pronounced in critically ill patients (9). Higher D-dimer levels were observed in non-survivors with COVID-19 compared to the survivors at hospital admission. Therefore, D-dimer monitoring will be helpful for patient triage and management. Several studies suggest that D-dimer

DOI: 10.33808/clinexphealthsci.1029009

levels greater than 1 µg/L may be implicated as a marker for severe COVID-19 and mortality (10).

The diagnosis of COVID-19 should be based on clinical and epidemiological history, etiological diagnostic tests that support the diagnosis of infection and/or complications. There are few studies showing the relationship between D-dimer and neutrophil/lymphocyte ratios (NLR) and COVID-19. Hematological and biochemical parameters are very important in the diagnosis, prognosis and clinical assessments of COVID-19. So, further and comprehensive studies are needed to clarify this topic. In this study, we aimed to evaluate the relation between D-dimer and NLR in patients with COVID-19.

2. METHODS

In this single centered retrospective study, a total of 2523 consecutive patients with COVID-19 (between 18-65 year) who were admitted to Karapınar State Hospital between March 2019 and July 2021 were enrolled in the study. The clinical characteristics and laboratory results were obtained. The measurement of D-dimer was performed with Mindray BS-800 (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China) clinical chemistry analyzer. D-Dimer concentration was determined by particle-enhanced immunoturbidimetric assay method. Hemogram parameters (neutrophil, lymphocyte, HGB, HCT etc.) were performed with Mindray BC-6800 (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China) heamology analyzer which analyzes complete blood count based on laser light scattering (forward and light scatter) and side fluorescent light. The approval of the research was obtained from the ethics committee of Necmettin Erbakan University Medicine Faculty (The date, 03.09.2021; the number, 2021/3375), and all the participants signed their consents before the study.

2.1. Statistical Analysis

To evaluate the data, SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used. JASP statistical package program was used to obtain the heatmap graph. In the study, descriptive statistics (mean, standard deviation, median value, minimum, maximum, number and percentile) were given for categorical and continuous variables. The relationship between two continuous variables was evaluated with the Pearson Correlation coefficient, and if the parametric test prerequisites were not linear, the Spearman correlation coefficient was used for evaluation. Less than 0.05 and 0.01 p values were considered as statistically significant.

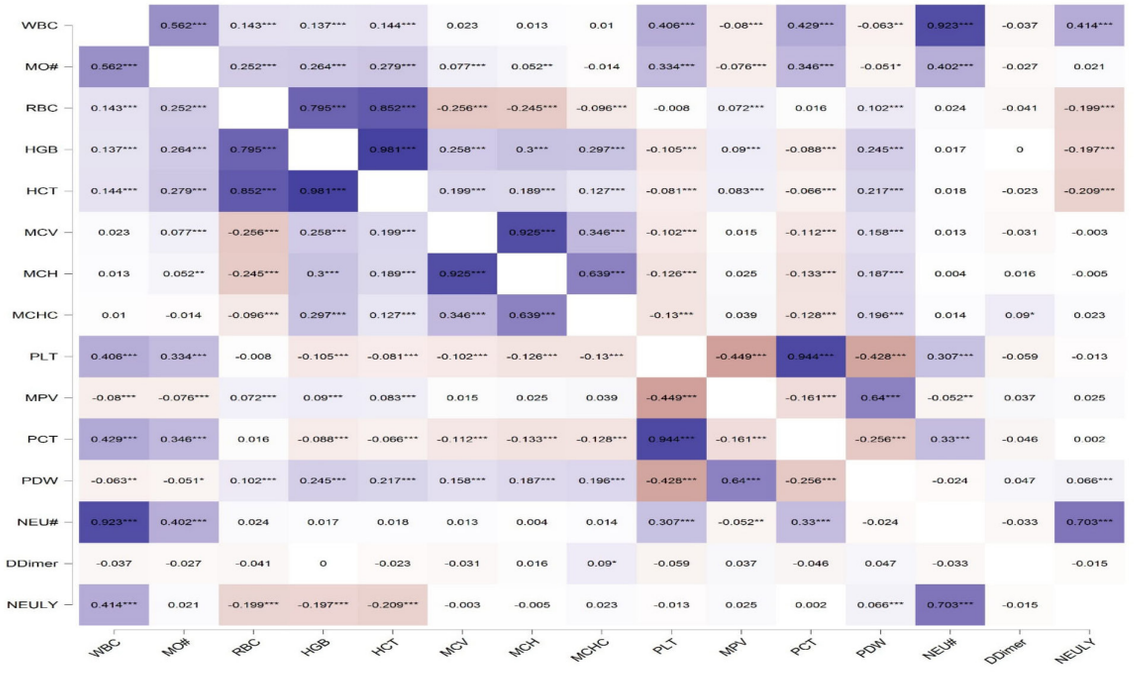

Figure 1. *Heatmap Graph (The heatmap graph shows correlations as symmetrically).*

Table 1. *Descriptive statistics of D-dimer and hemogram parameters in COVID-19 patients.*

Parameter	n	Minimum	Maximum	Mean	Std. Deviation
WBC, ($x10^9$/L)	2523	0.400	32.590	6.8819	2.9966
LYMPH#, ($x10^9$/L)	2523	0.000	7.150	1.5144	0.7543
LYMPH%, (CV%)	2523	0.000	63.500	24.0327	11.1627
MONO#, ($x10^9$/L)	2523	0.000	2.100	0.4523	0.2241
MONO%, (CV%)	2523	0.000	30.000	6.8864	2.8140
RBC, ($x10^{12}$/L)	2523	0.000	8.120	4.7111	0.6460
HGB, (g/dL)	2523	0.000	19.400	13.2141	1.8761
HCT, (%)	2523	0.000	65.800	39.7547	5.3874
MCV, (fL)	2523	0.000	124.900	84.5555	6.3561
MCH, (pg)	2523	0.000	43.900	28.1160	2.5354
MCHC, (g/dL)	2523	0.000	35.800	33.1893	1.3398
PLT, (10^3/µL)	2522	0.000	976.000	243.3727	101.0509
MPV, (fL)	2523	0.000	14.000	9.48962	1.1957
PCT, (%)	2523	0.000	0.830	0.2259	0.0837
PDW, (%)	2523	0.000	19.200	16.1481	0.6130
NEUT#, ($x10^9$/L)	2523	0.000	29.280	4.8242	2.8021
NEUT%, (CV%)	2523	0.000	96.900	67.6218	12.9114
EOS#, ($x10^9$/L)	2523	0.000	0.970	0.0757	0.1031
EOS%, (CV%)	2523	0.000	12.100	1.1440	1.4152
NLR	2521	0.298	69.484	4.2305	4.3313
D-dimer, (µg/mL)	627	100	10000	1236.664	1424.3491

WBC: White blood cell, LY#: Lymphocyte, LY%: Lymphocyte percentage, MONO#: Monocyte, MONO%: Monocyte percentage, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, NEUT#: Neutrophil, NEUT%:Neutrophil percentage,EOS#: Eosinophil, EOS%: Eosinophil percentage, NLR: Neutrophil/lymphocyte ratio

3. RESULTS

All inter-variable relations were evaluated with Spearman correlation coefficient. As shown in Table 1 and 2, there was a high correlation between the variables HCT and HGB, PLT and PCT, NEUT# and WBC, and MCH and MCV (r=0.981, r=0.944, r=0.923, r=0.925). In addition, there was a high correlation between RBC and HCT and between RBC and HGB variables (r=0.852, r=0.795). There was a moderate correlation between WBC and MO#, MCHC and MCH, PDW and MPV (r=0.562, r=0.639, r=0.64). All the relationships between these variables were positive, and the value of the correlated parameter increases linearly by unit as increases. According to Figure 1, the highest positive relationships were observed between HCT and HGB, PLT and PCT, NEUT# and WBC, MCH and MCV. No correlation was observed between D-dimer and NLR in patients with COVID-19 (r= – 0.015, p=0.49).

Table 2. *Relationships between D-dimer and hemogram parameters.*

		WBC	MO#	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	MPV	PCT	PDW	NEUT#	D-dimer
	r	.562**													
MONO#	p	0,001													
	N	2523													
	r	.143**	.252**												
RBC	p	0.001	0.001												
	N	2523	2523												
	r	.137**	.264**	.795**											
HGB	p	0.001	0.001	0.001											
	N	2523	2523	2523											
	r	.144**	.279**	.852**	.981**										
HCT	p	0.001	0.001	0.001	0.001										
	N	2523	2523	2523	2523										
	r	0.023	.077**	-.256**	.258**	.199**									
MCV	p	0.24	0.001	0.001	0.001	0.001									
	N	2523	2523	2523	2523	2523									
	r	0.013	.052**	-.245**	.300**	.189**	.925**								
MCH	p	0.508	0.009	0.001	0.001	0.001	0.001								
	N	2523	2523	2523	2523	2523	2523								
	r	0.01	-0.014	-.096**	.297**	.127**	.346**	.639**							
MCHC	p	0.623	0.489	0.001	0.001	0.001	0.001	0.001							
	N	2523	2523	2523	2523	2523	2523	2523							
	r	.406**	.334**	-0.008	-.105**	-.081**	-.102**	-.126**	-.130**						
PLT	p	0.001	0.001	0.685	0.001	0.001	0.001	0.001	0.001						
	N	2522	2522	2522	2522	2522	2522	2522	2522						
	r	-.080**	-.076**	.072**	.090**	.083**	0.015	0.025	0.039	-.449**					
MPV	p	0.001	0.001	0.001	0.001	0.001	0.446	0.205	0.05	0.001					
	N	2523	2523	2523	2523	2523	2523	2523	2523	2522					
	r	.429**	.346**	0.016	-.088**	-.066**	-.112**	-.133**	-.128**	.944**	-.161**				
PCT	p	0.001	0.001	0.432	0.001	0.001	0.001	0.001	0.001	0.001	0.001				
	N	2523	2523	2523	2523	2523	2523	2523	2523	2522	2523				
	r	-.063**	-.051*	.102**	.245**	.217**	.158**	.187**	.196**	-.428**	.640**	-.256**			
PDW	p	0.002	0.011	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001			
	N	2523	2523	2523	2523	2523	2523	2523	2523	2522	2523	2523			
	r	.923**	.402**	0.024	0.017	0.018	0.013	0.004	0.014	.307**	-.052**	.330**	-0.024		
NEUT#	p	0.001	0.001	0.225	0.381	0.357	0.501	0.826	0.494	0.001	0.009	0.001	0.229		
	N	2523	2523	2523	2523	2523	2523	2523	2523	2522	2523	2523	2523		
	r	-0.037	-0.027	-0.041	0	-0.023	-0.031	0.016	0.09*	-0.059	0.037	-0.046	0.047	-0.033	
D-dimer	p	0.355	0.5	0.312	0.999	0.564	0.436	0.698	0.02	0.144	0.366	0.244	0.248	0.41	
	N	627	627	627	627	627	627	627	627	627	627	627	627	627	
	r	0.041***	0.021	-0.199***	-0.197***	-0.209***	-0.003	-0.005	0.023	-0.013	0.025	0.002	0.066***	0.703***	-0.015
NLR	p	0.001	0.28	0.001	0.001	0.001	0.87	0.812	0.245	0.52	0.03	0.93	0.001	0.001	0.719
	N	2521	2521	2521	2521	2521	2521	2521	2521	2520	2521	2521	2521	627	627

*WBC: White blood cell, LY#: Lymphocyte, LY%: Lymphocyte percentage, MONO#: Monocyte, MONO%: Monocyte percentage, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, NEUT#: Neutrophil, NEUT%: Neutrophil percentage, EOS#: Eosinophil, EOS%: Eosinophil percentage, NLR: Neutrophil/lymphocyte ratio, *p<0.05, ** p<0.01,*** p<0.001*

4. DISCUSSION

From the beginning of the COVID-19 epidemic, the countries surrounding China became the epicenter of the epidemic, and then spread to the whole world that causes the death of millions of people. Scientific studies are very important in terms of struggle with COVID-19 disease (11). Therefore, clinical studies are mainly focus on COVID-19. In these clinical studies, determining the relationship of hemogram

and D-dimer may provide valuable information about the disease, and contribute to the diagnosis and prognosis (12).

The fibrinolytic system breakdown the fibrin system after the clot formation. The D-dimer, which contains the two D fragments of fibrin, is formed by the activation of the plasmin enzyme. This indicates the presence of a broken down fibrin in the bloodstream. Moreover, D-dimer represents activation of coagulation and fibrinolysis systems (13). As common, the D-dimer test is used in clinical practice to exclude the diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE) and to confirm the diagnosis of disseminated intravascular coagulation (DIC) (14, 15). De Monyé et al. declared that D-dimer levels are elevated in almost all patients with severe DVT. Also, D-dimer elevation may be observed in pathological and physiological conditions (16).

Many studies have been conducted examining the relationship between D-dimer levels and the severity of COVID-19 disease. In a case-control study, Spiezia et al. reported that forty-four COVID-19 patients had increased D-dimer levels with compared the control subjects (17). A recent study declared that D-dimer levels of non-intensive care unit and intensive care unit COVID-19 patients were determined as 1299 and 11.870 µg/L, respectively (18). In our study, D-dimer levels were determined as 1236.664 µg/mL in 627 COVID-19 patients. After hospitalization, elevated D-dimer levels of COVID-19 patients show persistence of multiorgan failure and a precursor to the development of disseminated intravascular coagulation (19). Moreover, a new study demonstrated that total antioxidant status and calculated oxidative stress index levels were correlated with CRP, fibrinogen and D-dimer levels (20). From the studies, it is stated that COVID-19 patients with D-dimer >1000 ng/ml have a 20 times higher risk of mortality which compared to those with lower D-dimer values (21). The D-dimer levels of COVID-19 patients was determined as 1236.664 µg/mL in our study (Table 1). In another study, D-dimer and CRP levels were found to be higher in those with pneumonia than in those without pneumonia (p=0.001 and p=0.001, respectively) (22).

Neutrophils are one of the vital immune cells of the human body. When pathogenic microorganisms invade the body, immune cells tend to rapidly provide chemotactic activation to the site of infection and play a role in host defense and immune regulation (23). Several studies were declared that neutrophils play an significant role in the pathophysiology of COVID-19, especially in the severity of disease. As similar with our study (4.8242x10^9/L), some reports highlight increased neutrophil levels in COVID-19 patients (3.4x10^9/L) (24, 25).

Lymphocytes are the main effector cells of the human immune response. The number of lymphocytes in the body is closely related to the body's immune and defense system against pathogenic microorganisms and negatively correlates with the degree of inflammation (26). As similar with the presented study (1.5144 x10^9/L), a study reported that lymphocyte levels were decreased in COVID-19 patients (1.3 x10^9/L) (27). Also, NLR were determined as 2.4 in patients with COVID-19, as similar with our study 4.2. In the study, we determined that there was no correlation between D-dimer and neutrophil/lymphocyte ratios of COVID-19 patients (r=-0.015, p=0.719 (Table 2). On the basis of our analysis, further studies with multi-centers are necessary to clarify these results.

5. CONCLUSION

Nowadays, D dimer levels and neutrophil/lymphocyte ratios are used for the evaluation of COVID-19 patients. As far as we know, the relation of D-dimer and neutrophil/lymphocyte ratios of COVID-19 patients were not evaluated in studies, yet. From the study, there was no relation between D-dimer and neutrophil/lymphocyte ratios of COVID-19 patients. In conclusion, more sample and prospective studies are needed to elucidate the relationship between D dimer and NLR in COVID-19 disease for clinical evaluations. The presence of comorbidity of the COVID-19 patients was not questioned. Also, patients with COVID-19 were aged between 18-65 years. As a retrospective study, our study has a limitation to obtain the all findings of the COVID-19 patients.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

The study approval was obtained from Necmettin Erbakan University Meram Faculty of Medicine, Non-interventional Clinical Trials Ethics Committee (approval number: 2021/3375)

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How to cite this article: Kader S, Akdag T, Sariyildiz L, Ozel Z. Evaluation of D-Dimer and Neutrophil/Lymphocyte Ratios of COVID-19 Patients Whom Applied to Karapınar State Hospital. Clin Exp Health Sci 2022; 12: 824-829. DOI: 10.33808/clinexphealthsci.1029009