Clinical Significance of the Relationship Between D-dimer and Erythrocyte Distribution Width in Covid-19 Patients

Covid-19 Hastalarında D-dimer ve Eritrosit Dağılım Genişliği Arasındaki İlişkinin Klinik Önemi

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ABSTRACT

Introduction: Red cell distribution width (RDW) is a marker that can be used in the presence of systemic inflammation and evaluating thromboembolic condition.We aimed to evaluate the relationship between RDW and the level of D-dimer known as related to adverse events in Coronavirus disease 2019 (COVID-19) in this study.

Methods: One hundred twenty two patients with COVID-19 and 62 healthy individuals with age and sex-matched were enrolled in the present study. The patients were divided into two groups based on evaluating their D-dimer level. The first group contained 45 patients with higher D-dimer level whereas the second group contained 77 patients with normal D-dimer level.

Results: RDWvalues were found to be higher in patients with COVID-19 and higher D-dimer level than patients with normal D-dimer level and control group. These results were found to be statistically significant (P=0.006 and P=0.013, respectively). Among patients with COVID-19, a positive correlation was observed between RDW and D-dimer level (r=0.270, P=0.003). Among the various variables associated with higher D-dimer in multivariate logistic regression analyses, RDW detected an independent predictor of higher D-dimer in COVID-19 patients (95% CI: CI:0.322-0.979, P=0.042).

Conclusion: The results indicated that high RDW values in patients with COVID-19 disease could be used as a marker in clinical follow-up of patients as D-dimer.

Key words: Red cell distribution witdh, D-dimer, marker

ÖZET

Giriş: Eritrosit dağılım genişliği (RDW), sistemik inflamasyon varlığında ve tromboembolik durumu değerlendirmede kullanılabilen bir belirteçtir. Bu çalışmada, Coronavirus hastalığı 2019'da (COVID-19) advers olaylarla ilişkili olduğu bilinen D-dimer düzeyi ile RDW arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Bu çalışmaya yaş ve cinsiyet açısından uyumlu 122 COVID-19'lu hasta ve 62 sağlıklı birey dahil edildi. Hastalar D-dimer düzeylerinin değerlendirilmesine göre iki gruba ayrıldı. Birinci grup D-dimer düzeyi daha yüksek olan 45 hastayı, ikinci grup ise normal D-dimer düzeyi olan 77 hastayı içeriyordu.

Bulgular: D-dimer düzeyi yüksek olan Covid-19 hastalarındaki RDW değerleri, D-dimer düzeyi normal olan Covid-19 hastaları ve kontrol grubuna göre daha yüksek bulundu. Bu sonuçlar istatistiksel olarak anlamlıydı (sırasıyla P=0,006 ve P=0,013). COVID-19 hastaları arasında RDW ile D-dimer düzeyi arasında pozitif bir korelasyon gözlendi (r=0.270, P=0.003). Çok değişkenli lojistik regresyon analizlerinde yüksek D-dimer ile ilişkili çeşitli değişkenler arasında RDW'nin, D-dimerin yüksek olduğu Covid-19 hastalarında bağımsız bir belirteç olduğu saptandı (%95 CI: CI: CI:0.322-0.979, P=0.042).

Sonuç: Sonuçlar, COVID-19 hastalığı olan hastalarda yüksek RDW değerlerinin D-dimer gibi hastaların klinik takibinde bir belirteç olarak kullanılabileceğini göstermiştir

Anahtar Kelimeler: Eritrosit dağılım genişliği, D-dimer, belirteç

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is among an important pandemic affecting the whole World nowadays. World Health Organization (WHO) reported COVID-19 as a novel coronavirus and defined its factor as severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) (1,2).It is known that infectious pathogens can trigger inflammatory response and thromboembolic events vital for host defence in patients with COVID-19. These incidents encountered especially in serious and critical cases can show themselves in various conditions such as myovascular thrombosis, venous, pulmonary thromboembolism and acute arterial thrombosis (3-6). Although, the pathogenesis of SARS-CoV-2 could not be well-defined, coagulation test abnormalities can be seen without bleeding signs in the

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Eskisehir Med. J. 2022; 3(2):123-129
Received date:04.03.2022 Accepted date:13.04.2022
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early stage of its infection. Among these tests, fibrinogen degradation products and an increase in the level of D-dimer are characteristic features. D-dimer analyses are the tests having low spesifity, high sensitivity and negative predictive value in cases with suspicious of thromboembolic disease (5-8).

Red cell distribution witdh (RDW) is a simple, cheap and easily accesible marker commonly used in clinical evaluations to measure variations in red blood cell size or red blood cell volume as part of a complete blood count (9). It is frequently used as a guide to diagnose anemia (iron deficiency and thalassemia trait). A normal range for red cell distribution width is 11.2 to 14 percent in adult females and 11.2 to 13.4 percent in adult males. In addition, existence of systemic inflammation and thromboembolic cases may lead to an increase in RDW (9,10). Literature studies are present related to RDW in patients with pulmonary embolism and venous thromboembolic cases and it was reported that there could be a relationship with thrombosis (11-13).

The aim of this study is to examine the changes in RDW and investigate its relationship with increased level of D-dimer during inflammatory period and thromboembolic cases in patients with COVID-19.

METHODS

One hundred twenty two patients with COVID-19 diagnosed by using real time polimer chain reaction (PCR) and thoracic computerized tomography (CT) and 62 healthy individuals with age and sex-matched were enrolled in the present study. The files and hospital records of the patients and healthy individuals were reviewed. The patients with COVID-19 were divided into two groups based on their D-dimer level. The first group contained 45 patients with higher D-dimer level whereas the second group contained 77 patients with normal D-dimer level (normal range:0-243 ng/mL). Among patients with COVID-19, patients with disorders of kidney and liver function, thyroid dysfunctions, diabetes mellitus, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, deficiency of vitamin B12 and folic acid were excluded from the study.

Laboratory Analysis

The complete blood count have been performed in the same analyzer, Mindray BC-6200, which is routinely checked every month in the central laboratory of our institution. Standard tubes with constant amount of ethylene diamine–tetra acetic acid have been used. The measurements of D-dimer level were determined quantitativly by a Coagulation Analyzer (ACL TOP 300) using latex enhanced immunoassay technique.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) 15.0 Package (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as arithmetic mean ± Standard deviation. The significance of the mean differences between groups was assessed by Student's *t*-test and one-way ANOVA. Differences were assessed by Chi-squared test for categorical variables. Relationships between variables were tested using Spearmen's correlation analysis. Receiver Operating Characteristic (ROC) curve graphics were used in the comparison of sensitivity and specificity. The effect of various variables on D-dimer high group in patients with COVID-19 was analyzed with logistic regression analyses. P values of less than 0.05 were regarded as significant.

RESULTS

It was observed that there was no significance between higher D-dimer and normal D-dimer patients with COVID-19 and control group in terms of gender and age (P=0.066 and P=0.977, respectively). RDW values were 14.03±1.48, 13.35±0.94 and 13.39±1.17 for

Table 1. Baseline clinical laboratory and demographic characteristics of D-dimer high and normal group in patients with COVID-19

	D-dimer high group in patients with COVID-19 (n=45)	D-dimer normal group in patients with COVID-19 (n=77)	*p* value
Age, years	54.4 ± 17.5	49.0 ± 12.5	0.055
Male/Female, n (%)	23(51.1) / 22(48.9)	31(40.3) / 46(59.7)	0.246
Ferritin, ng/mL	232.56 ± 245.59	160.20 ± 157.61	0.137
CRP, mg/L	37.79 ± 89.70	8.75 ± 9.27	0.046
INR	1.08 ± 0.24	1.07 ± 0.13	0.620
Leucocyte, $\times10^9$/L	5.28 ± 1.26	5.97 ± 2.07	0.072
Platelet, $\times10^9$/L	210.26 ± 58.98	215.24 ± 54.05	0.886
Hemoglobin, g/dL	12.99 ± 1.65	14.60 ± 1.90	<0.0001
RDW, %	14.03 ± 1.48	13.35 ± 0.94	0.006

All data mean±SD, RDW: Red cell distribution witdh, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, INR: International normalized ratio.

Table 2. Baseline clinical laboratory and demographic characteristics of D-dimer normal group in patients with COVID-19 and controls

	D-dimer normal group in patients with COVID-19 (n=77)	Controls (n=62)	*p* value
Age, years	49.0 ± 12.5	50.4 ± 5.9	0.782
Male/Female, n (%)	31(40.3) / 46(59.7)	31(50) / 31(50)	0.253
Leucocyte, $\times10^9$/L	5.97 ± 2.07	6.71 ± 1.30	0.026
Platelet, $\times10^9$/L	215.24 ± 54.05	247.66 ± 57.81	0.003
Hemoglobin, g/dL	14.60 ± 1.90	14.72 ± 1.26	0.907
RDW, %	13.35 ± 0.94	13.39 ± 1.17	0.987

All data mean±SD, RDW: Red cell distribution witdh, CRP: C-reactive protein.

D-dimer high group in patients with COVID-19, D-dimer normal group in patients with COVID-19 and control group, respectively. RDW values on D-dimer high group in patients with COVID-19 were found to be different from D-dimer normal group in patients with COVID-19 and control group. These results were found to be statistically significant (P=0.006 and P=0.013, respectively) (Figure 1). It was observed that there was no significant differences between D-dimer normal group in patients with COVID-19 and control group (P=0.987). Main laboratory properties of three groups were summarized in Tables 1 and 2.

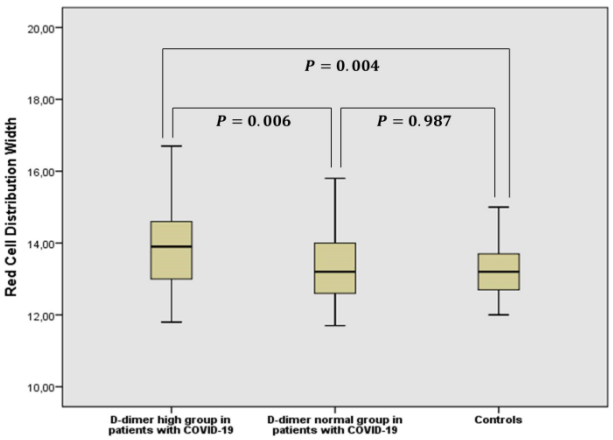

Figure 1. Comparison of red cell distribution witdh in covid-19 patients and control group.

A positive correlation was observed between RDW and the level of D-dimer in patients with COVID-19 disease (r=0.270, P=0.003) (Figure. 2). The results of correlation analysis are presented in Table 3. When assesing higher D-dimer levels of RDW was evaluated by ROC curve analyses among patients with COVID-19, a cut-off value was observed as 13.35 and sensitivity as 64%, specificity as 56% and P=0.001 (Area under curve:0.658, 95 % Confidence interval [CI] :0.566-0.749)(Figure. 3).

Among the various variables associated with higher D-dimer in multivariate logistic regression analyses, RDW remained an independent predictor of higher D-dimer in

COVID-19 patients (95% CI: CI:0.322-0.979, P=0.042). In addition, the gender was found to be significant of this patients. The results of multivariate logistic regression anlayses were presented in Table 4. Ethical approval was obtained from Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee with the date of 29.09.2020 and the number of 29.

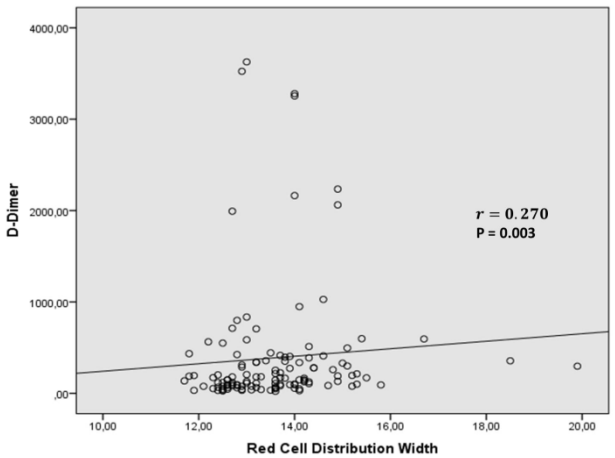

Figure 2. Correlation between D-dimer and red cell distribution witdh in COVID-19 patients.

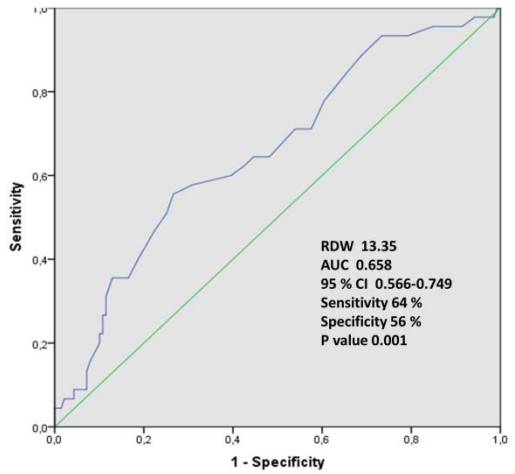

Figure 3. Receiver-operating characteristic curve of the red cell distribution witdh to predict D-dimer high group in COVID-9 patients.

DISCUSSION

In this study, corelations between the levels of RDW and D-dimer in patients with COVID-19 were evaluated. The values of RDW in higher D-dimer patients with COVID-19 were found to be higher than normal D-dimer patients with COVID-19 and control group. A positive correlation was observed between the levels of D-dimer and RDW in patients with COVID-19.

Table 3. The correlation between RDW and others parameters according to D-dimer in COVID-19 patients

	r	*p* value
Age, years	0.224	0.013
Ferritin, ng/mL	0.108	0.299
CRP, mg/L	0.384	<0.0001
Leucocyte, $\times 10^9$/L	-0.183	0.044
Platelet, $\times 10^9$/L	-0.080	0.379
Hemoglobin, g/dL	-0.380	<0.0001
RDW, %	0.270	0.003

RDW: Red cell distribution witdh, CRP: C-reactive protein

Although the pathogenesis of events resulted in making patients with COVID-19 prone to thrombosis and an increase in D-dimer levels was not fully identified, it was thought that several factors are responsible for this case (14). These are uncontrolled pro-inflammatory and anti-inflammatory responses during viral infections, epithelial cell dysfunction, an increase in the levels of hypoxia and blood viscosity in severe cases, generation of signalling pathways and thrombosis occuring as a result of increasing transcriptions factors dependant on hypoxia addition to comorbid status in patients, additional systemic diseases of patients, long-stay patient and applied invasive treatment (14,15). Moreover, sepsis and disseminated intravascular

coagulopathy can be developed during this process (16,17).

D-dimer occurs when fibrin clot produced during activation of coagulation system in the cruciate ligaments is broken by a plasmin. It is thouhgt that the level of D-dimer represents the dynamic equilibrium between curdling and lysis (18). It was reported that the risk of pulmonary embolism recurrence and recurrent venous thromboembolism in high D-dimer patients are high and therefore following the levels of D-dimer is suggested as a marker to evaluate the treatment of pulmonary embolism (19). Clinically, negative D-dimer tests exclude thromboembolic patients. Using this test reduces the necessity of applying additional interventional processes (20).

Table 4. Effects of various variables on D-dimer high in patients with COVID-19 in multivariate logistic regression analyses.

	Odds ratio	95 % Confidence Interval	*p* value
Age, years	1.008	0.970-1.048	0.684
Gender	0.273	0.087-0.859	0.026
Ferritin, ng/mL	0.998	0.994-1.002	0.325
CRP, mg/L	0.994	0.900-0.990	0.018
INR	1.061	0.018-63.861	0.977
Leucocyte, $\times 10^9$/L	1.252	0.902-1.738	0.179
Platelet, $\times 10^9$/L	0.998	0.988-1.009	0.720
RDW, %	0.561	0.322-0.979	0.042

RDW: Red cell distribution witdh, CRP: C-reactive protein, INR: international normalized ratio.

COVID-19 pneumonia, limited to the reported case reports, is evaluated as a triggering factor for venous thromboembolism and causal relationship in cases lacking predisposing factors (21,22).The level of D-dimer in patients with COVID-19 involves some limitations in itself for the determination of evaluating the thromboembolic situation. Because an increase in the levels of D-dimer can be observed in severe COVID-19 pneumonia without embolism and during the development of acute respiratory distress syndrome (23). In addition, it is known that high D-dimer level is always related to adverse events during the clinical progress of COVID-19 patients (24,25). Zhang et al.(17) in their study suggested that higher D-dimer levels in COVID-19 patients could be used as a marker to determine the mortality rates and clinic follow-up. Gao et al. (24) reported that high D-dimer levels not only were related with severe COVID-19 patients but also had clinical importance in estimating the level of seriousness of the disease in early stage. Leonard-Lorant et al. (25) found the levels of D-dimer high in patients with acute pulmonary embolism diagnosed by the pulmonary CT angiography. They also reported that raised D-dimer levels in COVID-19 patients could be the direct results of systemic inflammatory response sendrome, seconder high thrombosis activation or SARS-CoV-2 itself (25).

Recent studies showed that RDW was related with many thromboembolic cases and prognosis. Being part of complete blood cell count, RDW reflects the heterogeneity of red blood cell size as a marker for anisocytosis (26,27). The pathophysiology of anisocytosis and rising RDW levels in thromboembolic circumtances are still a matter of debate. Some evidences showed that it acts as acute phase reactants. Besides, in another hypothesis, it was suggested that RDW was related with raised prothrombothic effects of red blood cells and some genetic factors (27). Recents studies indicated that RDW was increased in relations with decreased oxygen saturation and hypoxemia. Hypoxia can increase bone marrow erythropoiesis by regulating the production of erythropoetin by kidney, resulting in releasing variable-size red blood cells in circulating system (28). Küçük et al. (11) determined that high RDW levels was an independent marker for mortality rates in acute

pulmonery thromboembolism. Sünnetçioğlu et al. (12) determined that RDW levels was found to be high compared with segmental involvement in patients with thrombus in the main pulmonary artery and that it was related with the levels of RDW and D-dimer in proximal thrombus immobilization. Çelik et al. (13) established that the levels of RDW and D-dimer were high in patients with pulmonary embolism and that RDW and D-dimer determined by the logictic regression analyses were independent predictors of pulmonary embolism. It was suggested that RDW could be used as a marker for diagnosing patients withpulmonary embolism (13).

Patients with COVID-19 are clinically classified in its entirety according to the intensity of symptoms. A few patiens can be entirely asemptomatic and the large part of patients can show lighter and moderate symptoms. Furthermore, severe cases in which hypoxemia findings can be seen and central cyanoses can be accompanied and critical cases leading to respiratory insufficiency and multiple organ failure can be observed (29). It is foreseen that changes occuring in RDW values could be important in our clinical practice when taken into account of the importance of the clinical progress and D-dimer levels in COVID-19 patients. In our study, RDW values in COVID-19 patients were found to be higher than normal D-dimer level patients and control group, relationship was observed between RDW and D-dimer levels in COVID-19 patients and higher D-dimer levels in patients was evaluated by ROC and logictic regression analyses. Based on these findings, it could be thought that RDW was important in COVID-19 patients and might be used as a useful marker in the clinical practice.

There were some limitations in our study. Among these were that it was a retrospective cross-sectional study, that patients with higher D-dimer level could not be evaluated by pulmonary CT angiography and that RDW values could not be evaluated in subgroups created by clinical classification due to the insufficient number of patients.

CONCLUSION

In summary, our study showed that there could be changes in RDW values of COVID-19 patients, these changes could be linked with D-dimer levels in COVID-19 patients and higher RDW values in COVID-19 patients could be used as a marker in the clinical practice as D-dimer. We believe that this study will guide the prospective multicentered studies evaluating the RDW values in COVID-19 patients.

Conflict of Interest: The author report no conflict of interest.

Financial Disclosure: No funding was taken for this study

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb;395(10223):497–506.

2. Tu Y-F, Chien C-S, Yarmishyn AA, et al. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Int J Mol Sci. 2020 Apr 10;21(7):2657.

3. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727–33.

4. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. Crit Care Med. 2020 May 27;Publish Ah.

5. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. Int J Lab Hematol. 2020 Jun 15;42(S1):19–20.

6. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 Jun;7(6):e438–40.

7. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003 Sep 25;349(13):1227–35.

8. Frater JL, Zini G, D'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020 Jun 15;42(S1):11–8.

9. Uslu AU, Yonem O, Aydin B, et al. Red cell distribution width is associated with albuminuria in adults with familial Mediterranean fever. Kaohsiung J Med Sci. 2016;32(4):216–20.

10. Ozsu S, Abul Y, Gunaydin S, Orem A, Ozlu T. Prognostic Value of Red Cell Distribution Width in Patients With Pulmonary Embolism. Clin Appl Thromb Hemost. 2014 May 8;20(4):365–70.

11. Pehlivanlar Küçük M, Öztuna F, Abul Y, et al. Prognostic value of red cell distribution width and echocardiographic parameters in patients with pulmonary embolism. Adv Respir Med. 2019 Apr 30;87(2):69–76.

12. Sunnetcioglu A, Sertogullarindan B, Ozbay B, Asker S, Ekin S. Assessments of the associations of thrombus localization with accompanying disorders, risk factors, D-dimer levels, and the red cell distribution width in pulmonary embolism. Clin (Sao Paulo). 2015 Jun 24;70(6):441–5.

13. Celik A, Ozcan IT, Gündes A, et al. Usefulness of admission hematologic parameters as diagnostic tools in acute pulmonary embolism. Kaohsiung J Med Sci. 2015 Mar;31(3):145–9.

14. Pan F, Yang L, Li Y, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci. 2020;17(9):1281–92.

15. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020 Jun 4;135(23):2033–40.

16. Kollias A, Kyriakoulis KG, Dimakakos E, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020 Jun 4;189(5):846–7.

17. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020 Jun 4;18(6):1324–9.

18. Eichinger S, Minar E, Bialonczyk C, et al. D-dimer levels and risk of recurrent venous thromboembolism. JAMA [Internet]. 2003 Aug 27;290(8):1071–4.

19. García Suquia A, Alonso-Fernández A, de la Peña M, et al. High D-dimer levels after stopping anticoagulants in pulmonary embolism with sleep apnoea. Eur Respir J. 2015 Dec;46(6):1691–700.

20. Hasegawa M, Wada H, Yamaguchi T, et al. The Evaluation of D-Dimer Levels for the Comparison of Fibrinogen and Fibrin Units Using Different D-Dimer Kits to Diagnose VTE. Clin Appl Thromb Hemost. 2018 May 8;24(4):655–62.

21. Tamburello A, Bruno G, Marando M. COVID-19 and Pulmonary Embolism: Not a Coincidence. Eur J Case Rep Intern Med. 2020;7(6):001692.

22. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Hear J. 2020 May 14;41(19):1858–1858.

23. Poggiali E, Bastoni D, Ioannilli E, Vercelli A, Magnacavallo A. Deep Vein Thrombosis and Pulmonary Embolism: Two Complications of COVID-19 Pneumonia? Eur J Case Rep Intern Med. 2020 Apr 8;7(5):1.

24. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020 Jul 10;92(7):791–6.

25. Leonard-Lorant I, Delabranche X, Severac F, et al. Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. Radiology. 2020 Apr 23;201561.

26. Uslu AU, Aydin B, Inal S, et al. The relationship between red cell distribution width and homozygous M694V mutation in familial Mediterranean fever patients. Ann Saudi Med. 2015 Mar;35(2):151–6.

27. Shahrbanoo Kheirkham-Sabetghadam, Yaser Jenab, Seyed-Mohammad Ghoreyshi-Hefzabad, et al. Association between elevated red blood cell distribution width and long-term mortality in acute pulmonary embolism. Turk J Med Sci. 2018 Apr 30;48(2).

28. Yčas JW, Horrow JC, Horne BD. Persistent increase in red cell size distribution width after acute diseases: A biomarker of hypoxemia? Clin Chim Acta. 2015 Aug;448:107–17.

29. Bulut C, Kato Y. Epidemiology of COVID-19. Turk J Med Sci. 2020 Apr 21;50(SI-1):563–70.

Cite as: Karagulle M. Clinical Significance of the Relationship Between D-dimer and Erythrocyte Distribution Width in Covid-19 Patients. Eskisehir Med J. 2022;3(2):123-129.