

INSPECTION OF THE D-DIMER / FIBRINOGEN RATIO ON THE FOLLOW-UP AND THE TREATMENT OF THE COVID-19 DISEASE

COVID 19 HASTALARININ TAKİP VE TEDAVİSİNDE D-DIMER FİBROJEN ORANININ İRDELENMESİ

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Anahtar Sözcükler: Covid 19, D - dimer / fibrinojen oranı, mortalite

Keywords: COVID-19, D-dimer / mibrinogen ratio, mortality

Yazının alınma tarihi: 29.09.2021

Kabul tarihi: 17.11.2021

Online basım: 23.02.2022

ÖZ

Giriş: Covid19 hastalığında trombo enflamatuvar patoloji nedeniyle birçok laboratuvar parametrelerinde değişiklikler olmaktadır. Pandemi viral enfeksiyonun patofizyolojisini hastalığın takip ve tedavisinde bilinmeyenleri ortaya çıkarmak için hastanemiz covid yoğun bakım ünitesinde takip edilen hastalarımızda rutin bakılan laboratuvar parametrelerinden D-dimer -fibrinojen parametreleri ile yaş ve mortalite ilişkisini irdeledik.

Gereç ve Yöntem: Hastanemiz covid yoğun bakımlarında Mart –Ağustos 2020 tarihlerinde Covid-19 enfeksiyonu nedeniyle takip ve tedavisi yapılan 260 hastadan kriterlerimize uyan 214 hastanın demografik özellikleri yoğun bakıma kabüllerindeki hemogram, biyokimya, prokalsitonin, crp, a-PTT, PT, fibrinojen, D-dimer, akciğer tomografileri komorbid hastalıkları tetkikleri mortaliteleri kayıt edilerek irdelendi.

Bulgular: Çalışmaya Covid19 enfeksiyonlu 260 hastadan kriterlerimize uyan 214 hasta dahil edildi. Hastaların genel yaş ortalaması 65,5±14,6 yıl min-max [18-96] olarak hesaplandı. Çalışmada, 65 yaş ve üstünde 135 (%63,1), 65 yaş altında 79 (%36,9) hasta bulunurken 113 (%52,8) erkek, 101 (%47,2) kadın hasta yer almıştır. Hastaların 51'i (%23,8) ex olurken 163'ü (%76,2) taburcu olmuştur. Çalışmanın ana odak noktası D-Dimer/Fibrinojen oranı olduğu için bu orana göre 1'in altında 156 (%72,9), 1 ve üstü orana sahip 58 (%27,1) hasta olduğu tespit edilmiştir. Yaş gruplarına göre ise 65 yaş ve üstündeki hastalar daha fazla ex olduğu gibi D-dimer/fibrinojen oranına bakıldığında 1 ve üstündekilerin ex olma durumu %64.7'lik oran ile 1'in altındaki orana sahip olanlara göre istatistiksel olarak anlamlı farklılık göstermektedir. Ayrıca D-dimer/fibrinojen oranı 1 ve üstü olanlarda yaşı 65 ve üstü olanların sayısı 52 (% 89.7), yaşı 65'in altında olanların ise 6 (%7.6) olarak bulunmuş ve aralarında istatistiksel olarak anlamlı fark vardır (p<0.001). D-dimer/fibrinojen oranına göre oluşan grup ile cinsiyet grupları arasında istatistiksel olarak anlamlı fark bulunmadı. (p>0.05).

Sonuç: Klinik olarak ağır seyreden COVID -19 hastalarında D-dimer-fibrinojen seviyesi artmış olmakla birlikte mortal seyreden hastalarda D-dimer /fibrinojen oranı 1 in üzerinde olması istatistiksel olarak anlamlı saptandı. D-dimer /fibrinojen oranının yüksekliği tedavide ileri tedavi yöntemlerine başlamamız için uyarıcı bir bulgu olabilir.

SUMMARY

Introduction: Thrombo-inflammatory pathology causes an alteration in several laboratory parameters in COVID-19 disease. In this study, one of the routinely followed laboratory parameters in the intensive care unit patients the D-dimer-fibrinogen parameters' connection with the age and mortality was inspected in order to reveal unknown knowledge about the pandemic viral infections follow-up, pathophysiology, and the treatment.

Materials and Method: From the 260 patients who were followed-up and treated in the ICU for COVID-19 in the period of March-August 2020, for 214 of patients that suit the inclusion criteria; their hemogram, biochemistry, procalcitonin, CRP, A-PTT, PT, fibrinogen, D-dimer, lung tomography, and demographic characteristics that routinely measured at the admission time, along with their comorbid diseases and necessary work-ups for their comorbid diseases were inspected and recorded.

Results: From 260 patients, 214 patients that suit the inclusion criteria were included in the study. The overall mean age of the patients was calculated as 65.5 ± 14.6 years min-max [18-96]. In the study, 135 (63.1%) patients aged 65 years or over, 79 (36.9%) patients aged below 65 years, while 113 (52.8%) men and 101 (47.2%) women were included. While 51 (23.8%) of the patients died, 163 (76.2%) were discharged. Since the main focus of the study was the D-Dimer / Fibrinogen ratio, it was determined that there were 156 (72.9%) patients below the ratio value of 1, and there were 58 (27.1%) patients with a ratio value of 1 or more. A statistically significant difference was stated in the D-dimer /fibrinogen ratios of the patients, death rates were found to be higher in those that had a value of 1 or higher along with a higher death rate in the age group of 65 years and over. In addition, among those with a D-dimer / fibrinogen ratio of 1 and above, distribution of the ages was found to be as such: 52 of them were 65 years of age and over (89.7%), 6 of them aged below 65 (7.6%), and it was stated as a statistically significant difference ($p < 0.001$). There was no statistically significant difference stated between the group formed by the D-dimer / fibrinogen ratio and the group formed by gender ($p > 0.05$).

Conclusion: Along with the increased value of the D-dimer-fibrinogen ratio, in clinically severe COVID-19 cases, D-dimer / fibrinogen ratio valued 1 or higher stated statistically significantly high in mortal patients. Increased D-dimer / fibrinogen ratio may be a cautionary finding for physicians to start advanced methods of treatment.

INTRODUCTION

COVID-19, also known as Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is an infection caused by a respiratory RNA virus that spreads via contact or droplets and was firstly identified in Wuhan City of China in December 2019 (1). While most of the cases that result from the pandemic are asymptomatic or experiences mild symptoms, the elderly population is experiencing more clinically serious conditions in terms of morbidity and mortality. It is thought that the thromboembolic-thromboinflammation and coagulation disorder pathophysiology causes the severe form of the disease. Even though at first ARDS like setting is seen, in most cases it develops into a multi-organ involved disease that causes high mortality rates (4).

Thrombo-inflammatory pathology causes an alteration in several laboratory parameters in COVID-19 disease (5). One of the parameters, fibrinogen; a glycoprotein, is an acute phase reactant that is synthesized by the liver, is important in clot forming and wound healing, and it functions in inflammation, malignancy, and

thromboembolic event. Another parameter that may be responsible for clinical setting off the disease is D-dimer. D dimer is a molecule that develops from fibrinogen in the clotting process with the degradation of fibrin by plasmin (fibrinolysis) that project thrombotic and fibrinolytic pathophysiology (6-7). COVID-19 infection is increasing many inflammatory markers and procoagulant factors including fibrinogen, and along with the D-dimer increase, it is thought that COVID-19 infection may be related to the coagulation anomalies (8). For solving and understanding the COVID-19-related coagulopathy, alterations in coagulation must be indicated by the measurable parameters, and studies are needed on this subject.

Coagulation test anomalies that are observed in SARS-CoV-2 infected patients are most likely to be a consequence of the thrombus forming triggered by the inflammation and disrupted fibrino-thrombotic response (9-10). Therefore, depending on the pathophysiology in the beginning, middle, and end of the infection, clinical projections of the anomalies in the "COVID-19 related coagulopathy" tests are

different (11). Regarding this subject, during the infection, significant increases in the prothrombotic and inflammatory substances are seemed to be balanced out with the increased fibrinolysis. To coherently evaluate this situation, the corresponding laboratory parameter D-dimer measurement is needed.

Pandemic causing COVID-19 infections mortality rate in the risk group of the elderly population is approaching to %30-38. This risk increases even more due to comorbid diseases that develop more with age (12-13). Clinical and laboratory findings, particularly the measurements in the hemogram and the coagulation parameters designate the protocol, density, and the method of the treatment (14).

This study aims to document the demographic characteristics and the D-dimer / fibrinogen laboratory parameter of the 214 cases hospitalized in the intensive care unit where severe cases infected with COVID-19 is being followed-up; and is to research the effects of their connections on mortality.

MATERIALS AND METHOD

Scientific research study approval no. 2020-05-03 T18-01-03 was received from the Ministry of Health for our study. After the approval of the Ministry, Bozyaka Training and Research hospital was planned with the ethical permission of the ethics committee 21/05/2020-222

Patients included to the study accordingly with the criteria of:

Inclusion Criteria of the Study

- (1) Those who suit the clinical and epidemiologic case definition
 - i) FPBP (fever, pulse, blood pressure values) and respiratory symptoms
 - ii) Typical CT image abnormalities of viral pneumonia
 - iii) A positive result of RT-PCR for SARS-CoV-2 RNA
 - iv) Taking sputum and throat-nose swabs at admission and testing it within 3 hours with real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA positivity.

Exclusion Criteria of the Study

- 1) Patients with haematological and oncological follow-up or patients who were immunosuppressive for any other reason were excluded from the study.

Clinical features and laboratory data, epidemiological characteristics of patients including contact history, clinical symptoms, and laboratory findings were obtained from the electronic medical records. The severity of the COVID-19 is defined pursuant to the international guidelines of community-acquired pneumonia. The endpoint of the study is defined as the criteria of discharge from the ICU/the hospital or death in 28 days.

From the 260 patients who were followed-up and treated in the ICU for COVID-19 in the period of March-August 2020, for 214 of patients that suit the inclusion criteria; their hemogram, biochemistry, procalcitonin, CRP, A-PTT, PT, fibrinogen, D-dimer, lung tomography, and demographic characteristics that routinely measured at the admission time, along with their comorbid diseases and necessary work-ups for their comorbid diseases were inspected and recorded.

RESULTS

The study included 260 patients who were followed up with the diagnosis of covid 19 in our hospital's covid 19 intensive care unit between March-August 2020, and 214 patients who met our study criteria. Pregnant women, patients under the age of 18, patients under the age of 18, those receiving immunosuppressive treatment, those receiving oncological treatment, and patients with haematological malignancies were excluded from the study

214 patients diagnosed with COVID-19 were included in the study. The overall mean age of the patients was calculated as 65.5 ± 14.6 years, min-max (18-96). In the study, 135 (63.1%) patients aged 65 years or over, 79 (36.9%) patients aged below 65 years, while 113 (52.8%) men and 101 (47.2%) women were included. While 51 (23.8%) of the patients died, 163 (76.2%) were discharged. Since the main focus of the study was the D-Dimer / Fibrinogen ratio, it was determined that there were 156 (72.9%)

patients below the ratio value of 1, and there were 58 (27.1%) patients with a ratio value of 1 or more.

Comparison of COVID-19 related mortality and biochemistry parameters is shown in the Table 1. Important parameters that show a significant alteration on the survival are as follows: PDW, D-Dimer, Fibrinogen, LDH, Glucose, Urea, Creatinine, ALT, AST, APTT, CK, Total-Bilirubin and CRP.

Deceased patients' D-dimer and fibrinogen parameters, when evaluated with the ROC analysis, cut-off values, and sensitivity-specificity ratios by mortality are shown in the table 2. It is seen that the D-dimer parameter is a powerful marker (graph1). The correlation between the d-dimer and the fibrinogen were inspected, and a statistically significant connection was determined ($r=0.792$; $p<0.001$).

As seen in the table 3. %30 more cases of death were observed in men than women. However, this finding is not statistically significant. When evaluated by the D-dimer/fibrinogen ratio, a statistically significant difference was found in the matter of more deaths were observed in patients that had a value of 1 and over with a rate of 67.7, than the patients that had a value below 1. When evaluated by age, it was seen that patients aged 65 and above showed more cases of death than the patients aged below 65 years. In an addition to these findings, in patients that had a value of 1 and over, the portion of the patients aged 65 and over were found 52 (%89.7), and the portion of the patients aged below the 65 years was found 6 (%7.6), and a statistically significant difference was found between these ($p<0.001$). There was no statistically significant difference stated between the group formed by the D-dimer / fibrinogen ratio and the group formed by gender ($p> 0.05$).

Table 1. Comparison of the biochemistry parameters by mortality on COVID-19 patients (N=214)

Parameters	EX (n=51)	LIVE (n=163)	p Value
Hemoglobin	2.5±2.2	1.4±2.8	<0.001
RDW	2.8±4.2	2.2±5.6	0.853
PDW	2.9±3.5	1.8±7.6	<0.001
D-DIMER	5520.0±10799.8	238.4±952.4	<0.001
Fibrinogen	884.0±307.3	605.4±213.7	<0.001
LDH	122.6±242.2	17.7±50.1	<0.001
Glucose	87.2±79.2	22.2±33.6	<0.001
Urea	82.4±53.9	7.3±14.1	<0.001
Kreatinin	11.8±6.8	8.5±11.9	0.002
ALT	165.6±436.4	12.2±25.5	0.001
AST	213.4±560.5	8.7±11.0	<0.001
PT	15.6±21.4	8.9±12.1	0.812
APTT	34.6±15.2	29.7±4.3	0.023
INR	2.4±2.7	1.9±3.2	0.702
CK	341.0±766.1	8.5±32.1	<0.001
Bilirubin-Total	11.1±16.9	3.6±3.2	0.042
CRP	620.2±901.8	161.1±282.9	0.001
Ferritin	246.5±389.7	102.4±297.7	0.303

*Independent t-test was used and $p<0.05$ was considered significant.

Table 2. Comparison of parameters by mortality

Parameters	Cut-off Value	AUC	p-Value	CI [min-max]	Sensitivity (%)	Specificity (%)
D-Dimer*	321.5ng/mL	0.905	<0.001	0.863 0.946	92,2	74.2
Fibrinogen	698.5mg/dL	0.768	<0.001	0.691 0.846	70.6	68.7

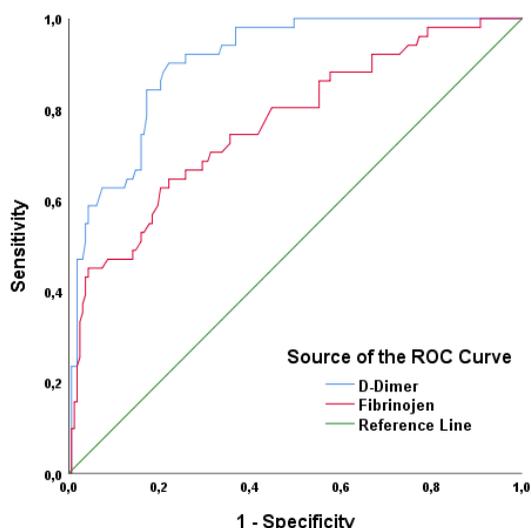
AUC; Area Under Curve, CI; confidence Interval (95%), $p<0.05$ was considered significant.

* Strong parameters for taking into the mortality

Table 3. Compare of parameters between ex and live patients (n=214)

Parameters	Subgroups	Survival		p-value	χ^2
		Ex	Live		
		n(%)	n(%)		
Gender					
	Male	32 (62.7)	81 (49.7)	0,103	2,655
	Female	19 (37.3)	82 (50.3)		
Age					
	<65	7 (13.7)	72 (44.2)	<0,001	15,462
	>=65	44 (86.3)	91 (55.8)		
D-Dimer/Fibrinogen					
	<1	18 (35.3)	138 (84.7)	<0,001	47,92
	>=1	33 (64.7)	25 (15.3)		

Pearson's Chi Square test was used and p<0.05 was considered significant.



Graph1. ROC Analysis for D-Dimer and Fibrinogen

DISCUSSION

COVID-19 infection is a situation of entity and morbidity, characterized by triggering the thrombo-inflammatory reactions, and the microthrombi that formed by complex physiopathological pathways determine the severity of the infection in severe cases that may result in death (15).

In the study of Chen N et al., it was seen that in the first 99 patients hospitalized in Wuhan; %6 had prolonged APTT, %5 had prolonged prothrombin time, %36 had increased fibrinogen D-dimer, along with increased interleukin 6,

increased CRP, and elevated sedimentation rate (16). Also in that study, the mortality rate in patients with increased fibrinogen, d-dimer, and elevated coagulation parameters, was found considerably higher. In this study, in patients admitted to the ICU, initial d-dimer and fibrinogen levels were elevated and a high D-dimer/fibrinogen rate along with D/F rate being valued higher than 1 had increased mortality even higher.

In a study conducted by the Tang N et al., (17) in 449 patients with COVID-19, in patients with an elevated d-dimer level and in patients treated with enoxaparin (40-50mg) that had a coagulopathy, mortality rates were found %40 and %64,6 respectively. Especially, in the group with elevated d-dimer levels, the mortality was found %20 lower after treated with prophylactic dosage heparin. Along with emphasizing the fact that in the patients with elevated coagulation parameters, heparinization lowers the mortality rates; it was also stated that the elevated D-dimer and fibrinogen are related to high mortality. In this study, increased mortality in patients with high d-dimer/fibrinogen were found coherently and mutual.

In a study conducted by Wang D et al. it is emphasized that values of D-dimer, PT, APTT, fibrinogen, and platelet count measured at the admitting time, along with the elevated D-dimer and fibrinogen levels in death cases after their follow-up for 7 to 10 days; are related with bad

prognosis of the disease in patients with COVID-19 (18).

In a study about fibrinogen/albumin, and platelet count in COVID-19 infection conducted by the Xiaojie Bi et al., results have shown that coagulation parameters differ considerably among the clinically severe and clinically mild patients (19). It was seen that in clinically severe patients, even at an early stage of the disease along with thrombocytopenia and elevated levels of fibrinogen/albumin, fibrinogen and d-dimer increase is becoming more significant as the disease worsens. It was seen that in the patients who died because of the COVID-19 had significantly higher levels of D-dimer in their last follow-up.

In a study conducted by the Christopher D et al. in Italy, it was stated that the fibrinogen and D-dimer levels are closely involved in the thrombosis, when the fibrinogen levels reach above to the 800-900mg/dl, the viscosity of the blood increases 3 times, and the physiologic stasis of the Virchow's thromboembolic reactions are contributing to the thrombus formation and to the hypercoagulability endothelial damage (20). Increased coagulability caused by hyper fibrinogenaemia and other elevated procoagulant substances have a notable impact on the thromboembolic events that occur in ARDS. Post-mortem COVID-19 autopsy findings support this case. As a result of this, in their study, they claimed that early intervention to the microvascular thrombosis in the organs and tissues with an effective anticoagulant can have an important impact on preventing and treating the ARDS and the multiple organ dysfunction syndrome.

In cases that included in this study, it was seen that in the treatment and follow-up of the increase in the D-dimer/fibrinogen ratio that primarily measured at the admitting time was causing high mortality. In clinically severe patients along with

the increased d-dimer/fibrinogen ratio, in mortal patient's value of the d-dimer/fibrinogen ratio was found over 1. This ratio's increase in prevalence was found statistically significant. This study supports that increased fibrinogen and d-dimer levels are considerably related to the mortality and have an impact on basic pathophysiology along with a faster and higher increase in d-dimer relative to the increase in fibrinogen is a marker of the density of the thromboembolic and thrombolysis pathway. High d-dimer and fibrinogen levels measured at the admission and higher d-dimer and fibrinogen levels were measured after the follow-up of the patients in the ICU show that high d-dimer levels measured at the first admission are related to the increase in the mortality caused by COVID-19. Although COVID-19 associated coagulopathy is rarely connected with an important bleeding issue, accepted opinion on COVID-19-associated coagulopathy is that it causes thrombus formation (21). Because the disrupted coagulation parameters have an effect on the mortality, a close follow-up of these parameters is a warning to start advanced COVID-19 treatments and effective coagulant treatment. Because the increased D-dimer / fibrinogen ratio is directly correlated with the severity of the infection and with the mortality, the increased value of this ratio may be a cautionary finding for us to start advanced methods of treatment.

CONCLUSION

Along with the increased value of the D-dimer-fibrinogen ratio, in clinically severe COVID-19 cases, D-dimer / fibrinogen ratio valued 1 or higher stated statistically significantly high in mortal patients. Increased D-dimer / fibrinogen ratio may be a cautionary finding for physicians to start advanced methods of treatment. More studies are needed in terms of evaluating the advanced treatments for COVID-19 infection's follow-up and treatment.

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