RESEARCH ARTICLE

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The Relationship between COVID-19 Suspected Patient's Coagulation and Platelet Parameters and Polymerase Chain Reaction Results

ABSTRACT

Objective: This study aims to investigate the relationship between prothrombin time (PT), activated partial thromboplastin time (aPTT), INR (International Normalized Ratio), and D-dimer levels, platelet (PLT) levels at hospital admission, and positivity or negativity of Polymerase Chain Reaction (PCR) test results in patients with suspected coronavirus disease-19 (COVID-19) followed at COVID-19 services.

Methods: This study was performed on 238 patients with the prediagnosis of COVID-19, all patients are hospitalised in Samsun city at our hospital between 11 March 2020-30 May 2020. According to COVID-19 PCR test results, PCR test negative 119 individua and PCR test positive 119 patients were included in the study. PT, aPTT, D-dimer, INR, and PLT levels were examined.

Results: While PCR test negative individuals had a mean PT value of 11.46±0.86 sec, PCR test positive patients had a mean PT value of 12.97±3.65 sec ($p<0.001$). There was no significant difference in mean aPTT values of PCR test positive and negative patients. Whereas INR, D-dimer increased significantly in PCR test positive patients. PLT value decreased from a mean value of 266.75±71.36*10^9/L in PCR test negative patients to 241.18±96.64*10^9/L in PCR test positive patients ($p=0.002$).

Conclusions: In our study, it was found that in patients who were admitted to hospital with COVID-19 suspicion and followed up in COVID-19 services, PT, D-dimer, INR, PLT values were important in detecting coagulopathy and thrombocytopenia in the group who were PCR positivity.

Keywords: COVID-19, PT, aPTT, D-dimer, INR, PLT, PCR Test.

COVID-19 Şüphesi Taşıyan Hastaların Koagülasyon ve Trombosit Parametreleri ile Polimeraz Zincirleme Tepkimesi Sonuçları Arasındaki İlişki

ÖZET

Amaç: COVID-19 şüphesi ile COVID-19 servislerinde takip edilen hastaların, hastaneye başvuru sırasında yapılan Protrombin Zamanı (PT), aktive Parsiyel Tromboplastin Zamanı (aPTT), INR (International Normalized Ratio), D-Dimer düzeyleri, Trombosit (PLT) düzeyleri ile Polimeraz Zincirleme Tepkimesi (PCR) sonucunun pozitif veya negatif durumu arasındaki ilişkiyi araştırmak amaçlanmaktadır.

Gereç ve Yöntem: Bu çalışma 11 Mart 2020- 30 Mayıs 2020 tarihleri arasında, Samsun ilinde, hastanemizde COVID-19 şüphesi ile yatan 238 hasta ile yapılmıştır. COVID-19 sonuçlarına göre PCR testi negatif 119 kişi ve PCR testi pozitif 119 hasta çalışmaya dahil edilmiştir. PT, aPTT, D-dimer, INRve PLT düzeylerine bakılmıştır.

Bulgular: PT; PCR testi negatif katılımcılarda ortalama 11,46±0,86 sn değeri bulunurken, PCR testi pozitif hastalarda 12,97±3,65 sn, ($p<0,01$), aPTT; PCR negatif katılımcılarda ortalama 24,38±3,40 sn, PCR pozitif hastalarda ise 24,18±4,83 sn,($p>0,05$) olarak bulunmuştur. D-Dimer, PCR testi negatif katılımcılarda ortalama 0,23±0,12 µg/ML, PCR testi pozitif hastalarda ise 2,10±5,60 µg/ML, ($p<0,01$) olarak tespit edilmiştir. INR; PCR negative katılımcılarda 0,99±0,12 değeri, PCR pozitif hastalarda ise 1,14±0,35, ($p<0,01$) değeri bulunmuştur. PLT; PCR testi negative katılımcılarda 266,75±71,36 (10^9/L), PCR testi pozitif hastalarda ise 241,18±96,64 (10^9/L) olarak saptanmıştır ($p=0,002$).

Sonuç: Çalışmamızda, hastaneye COVID-19 şüphesi ile başvuran, COVID-19 servislerinde takip edilen, PCR pozitif olan hastalarda, PT, D-Dimer, INR, PLT değerlerinin, koagülopati ve trombositopeni tespitinde önemli olduğu saptandı.

Anahtar Kelimeler: COVID-19, PT, aPTT D-dimer, INR, PLT, PCR Test.

INTRODUCTION

COVID-19 which shares similarities with SARS (Severe Acute Respiratory Syndrome) and Middle East Respiratory Syndrome (MERS) viruses responsible for endemic diseases in 2003 and 2012, is a novel beta coronavirus (1,2). In addition to being a critical disease for health, coronavirus 2019 (COVID-19) poses a global threat (3).

First, pneumonia cases of unknown etiology occurred in Wuhan, Hubei province of China; the cases were reported to WHO (World Health Organization) in December 2019, and in March 2020, WHO declared this new infection a pandemic (4,5).

COVID-19 is described as a new betacoronavirus. It is closely related to SARS. It is a new infectious disease in which the virus is the causative pathogen 5. Despite pulmonary pathophysiology during the disease, severe COVID-19 infection, which is not fully understood, is associated with pronounced alveolar inflammatory cell infiltration and is accompanied by systemic cytokine storm (6). One of the essential poor prognosis indicators is the development of coagulopathy in patients (7,8,9). Increased plasma levels of fibrin degradation D-dimers with COVID-19 infection constitute an independent biomarker for poor prognosis (9). In the COVID-19 pathogenesis of coagulation activation, significant pathological changes involving lung microvasculature including widespread microthrombus and significant hemorrhagic necrosis have been highlighted, particularly in line with post-mortem studies (10,11).

Severe COVID-19 increases the risk of developing significantly associated deep vein thrombosis and pulmonary embolism (12,13). For estimating the severity of COVID-19, monitoring functional screening parameters for PLT, PT, aPTT, and D-D (D-dimer) and daily changes in coagulation function is essential in patients with COVID-19 (14).

The poor prognosis that continues with COVID- 19 and continuation of D-dimer increase are precursors of multiorgan failure and development of DIC (Disseminated Intravascular Coagulation) (15). Significantly, a high D-dimer level is associated with increased mortality. In patients who lost their lives, the increase is evident from the fourth day of hospitalization. Despite coagulopathy, hemorrhage findings are not a common biomarker (15,16,17).

MATERIAL AND METHODS

Study Design and Participants: The study was carried out in the COVID-19 services of the Samsun University Samsun Training and Research Hospital between March 11, 2020 and May 30, 2020. Patients with COVID-19 symptoms were included in the study. The PCR results were divided into two groups as PCR positive and PCR negative, in line with the World Health Organization's guideline titled "Laboratory Testing for 2019 Novel Coronavirus (2019-nCoV) in Suspected Human Cases" published on March 2, 2020.

All samples were studied with the SARS CoV-2 Double Gene RT-q PCR Kit (BioSpeedy, Turkey) following the manufacturer's instructions. Briefly, after nucleic acid isolation in nasopharyngeal lavage/aspirate, bronchoalveolar lavage, nasopharyngeal suture, oropharyngeal swab and sputum samples, detection by single-step reverse transcription (RT) and Real-Time PCR targeting the ORF1ab and N gene regions were performed.

Extract ion and inhibition control were checked by targeting the human RNase P gene as an internal control. Nucleic acid extraction was validated with the vNAT buffer, and this process was conducted without any additional work during sample transfer. Nasopharyngeal or oropharyngeal swab samples taken with swabs (dacronor polyester flock) were placed in a sterile transport solution containing vNAT solution and transferred. Reaction components 2X Prime Script mix 10µL, CVD Di Oligo mix 5µL, template nucleic acid 5µL total reaction amount of 20µLvolume was created. Qiagen Rotor-Gene (Germany) Real-Time PCR instrument was run on sigmoidal curves under 38 cycles and were evaluated as positive.

Prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, International Normalized Ratio (INR), and platelet (PLT) levels of 119 patients followed in COVID-19 services were taken from the hospital information management system. In addition, PT, aPTT, D-dimer, INR, and PLT levels of 119 individuals with COVID-19 PCR test negative were taken.

D-dimer test was worked on a Beckman Coulter Au 680 device, PT, aPTT, and INR tests were worked at Siemens Ca-7000 device, and platelet level was worked in Beckman Coulter Dx-800 device by using suitable tubes and kits.

Ethical Approval: Ethical approval to conduct this study was granted by the hospital's ethics committee on September 30, 2020 (decision number GOKA/2020/9/10).

Data Analysis: Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA) was used for the data analysis in the present study. One-Sample Kolmogorov – Smirnov test and the Shapiro-Wilks test were used to evaluate the data. Mann–Whitney U-test was used to compare parameters between the groups. A $p < 0.05$ was considered to be statistically significant. G*Power 3.1.9.7 program was used to calculate the sample size. One hundred ten sample size results were obtained for each group, in this calculation (test=t-test (Wilcoxon-Mann-Whitney test (two groups)), Analysis: A priori: Compute required sample size, Tail(s) =Two, Parent distribution=Normal, Effect size

d=0.5, α err prob=0.05, Power (1-β err prob)=0.95, Allocation ratio N2/N1=1).

RESULTS

According to the results of combined oropharyngeal/ nasopharyngeal swab test performed, 119 patients were PCR-positive and 119 patients were PCR-negative. The mean age of the PCR positive patients was 58.29 (SD, 10.10) years. Some 50.4% (n=60) of the PCR positive patients were women. Complaints of the PCR positive patients with suspicious contact admitted to our hospital were respiratuar distres (48.2%), loss of smell (16.8%), loss of taste (12%) (Table 1).

Tablo 1. Descriptive characteristics of individuals (n=238)

Categorical variables		**COVID-19(+)**	**COVID-19 (-)**
n (%)		119	119
Age±SD		58.29±10.10	41.08±9.71
Hospitalization day		15.92	6.84
Gender (n, %)	Male	59 (49.6)	84 (70.6)
	Female	60 (50.4)	35 (29.4)
Intensive care unit (n, %)	Yes	44 (63.0)	-
	No	75 (37.0)	119
Ex-Discharge	Ex	28 (23.5)	-
	Discharge	91 (76.5)	119
Comorbidity (n,%)	Cancer	7 (5.9)	3 (2.5)
	DiabetesMellitus	22 (18.5)	24 (20.2)
	Hypertension	21(17.6)	18 (15.1)
	Cardiovascular disease	11 (9.2)	4 (3.4)
	Chronicrenalfailure	9 (7.6)	2 (1.7)
	Pneumonia	15 (12.6)	8 (6.7)
	COPD	6 (5.1)	7 (5.9)
	No	28 (23.5)	53 (44.5)
Signs and symptoms (n,%)	Respiratory Distress	34 (28.6)	0
	Loss of Smell	20 (16.8)	3 (2.5)
	Loss of Taste	12 (10.0)	0
	Fever	38 (32.0)	17 (14.3)
	Headache	28 (23.5)	34 (28.6)
	Joint Pain	29 (24.4)	17 (14.3)
	Weakness	36 (30.3)	50 (40.0)
	Cough	15 (12.6)	17 (14.3)
	Anorexia	5 (4.2)	2 (1.7)
	Nausea	3 (2.5)	0
	Diarrhea	2 (1.68)	0

The test reference range of the samples analyzed in Biochemistry Laboratory was taken as 10-14 seconds (sec) for prothrombin time (PT). While the mean of PT value was found to be 11.46±0.86 sec, in PCR negative individuals, the mean of PT value was found to be 12.97±3.65 sec. in PCR positive patients. A statistically difference was observed between the mean of PT values and the gender variable (p<0.001) (Table 2).

Table 2. The association between PT, aPTT, D-dimer, INR, PLT levels by gender and COVID-19 results.

Gender	**PCR (n)** / **Statistical values**	**PT±SD (sec)**	**aPTT±SD (sec)**	**D-dimer±SD (µg/ml)**	**INR±SD**	**PLT±SD (*10^9/L)**
Male	**Negative (84)**	11.53±0.93	24.75±3.52	0.22±0.10	0.99±0.13	253.36±64.15
	Positive (59)	13.19±3.25	25.40±5.52	2.29±6.27	1.16±0.30	228.07±91.60
	U	**1027.000**	**2449.000**	**378.500**	**1035.000**	**1893.500**
	P	**<0.001**	**0.905**	**<0.001**	**<0.001**	**0.017**
	Effect size	**0.50**	**0.01**	**0.72**	**0.50**	**0.20**
Female	**Negative (35)**	11.29±0.65	23.49±2.96	0.27±0.12	0.99±0.06	298.89±78.22
	Positive (60)	12.75±4.02	22.98±3.72	1.91±4.91	1.13±0.39	254.08±100.45
	U	**605.500**	**962.000**	**322.000**	**589.500**	**641.500**
	P	**0.001**	**0.497**	**<0.001**	**<0.001**	**0.002**
	Effect size	**0.35**	**0.07**	**0.58**	**0.37**	**0.32**
Total	**Negative(119)**	11.46±0.86	24.38±3.40	0.23±0.12	0.99±0.12	266.75±71.36
	Positive (119)	12.97±3.65	24.18±4.83	2.10±5.60	1.14±0.35	241.18±96.64
	U	**3765.500**	**6446.000**	**1457.500**	**3616.000**	**5435.500**
	P	**<0.001**	**0.232**	**<0.001**	**<0.001**	**0.002**
	Effect size	**0.40**	**0.07**	**0.69**	**0.42**	**0.20**

U=Mann-Whitney U value. p =AsymptoticSig. (2-tailed test).

The test reference range of the samples analyzed in Biochemistry Laboratory was taken as 18-36 seconds (sec) for activated partial thromboplastin (aPTT). While the mean of aPTT value was found to be 24.38±3.40 sec. in PCR negative individuals, the mean of aPTT value was found to be 24.18±4.83 sec in PCR positive patients. No statistically significant difference was observed between the two groups (Table 2). The test reference range of the samples analyzed in Biochemistry Laboratory was 0-0.5 µg/ml for D-dimer. While the mean of D-dimer value was found to be 0.23±0.12 µg/ml in PCR test negative individuals, the mean of D-dimer value was found to be 2.10±5.60 µg/ml in PCR positive patients. There was a significant difference between D-dimer, INR, PLT values of the two groups (p values were <0.001,<0.001,0.002, respectively) (Table 2). In our study, the relationship between PT, aPTT, D-dimer, INR, PLT levels according to the PCR positive group and gender was evaluated. There was a significant difference between the mean of PT values and the gender variable (p<0.001) (Figure 1).

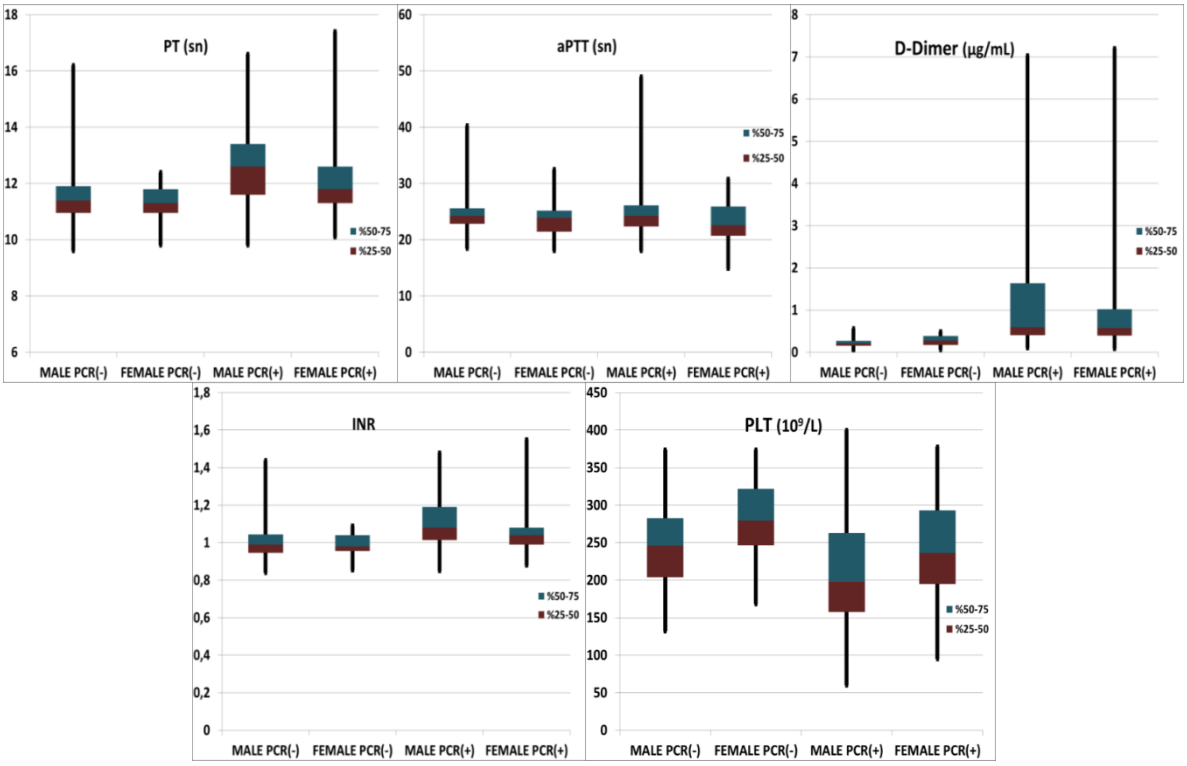

Figure 1. The association between PT, aPTT, D-DIMER, INR, PLT levels according to gender COVID-19 results in boxplots

Forty four patients in our hospital's COVID-19 intensive care unit included in the study, these patients were admitted to the intensive care unit for reasons such as respiratory failure, shock or the need for mechanical ventilation support while being monitored. During the period of inpatients, Metilprednisolon and Enoksaparin sodyum were given in the treatment of anticoagulants based on the guidance published by the Ministry of Health called COVID-19.

DISCUSSION

This study, which we conducted in our research hospital in the first months of the pandemic, showed that PT, D-dimer, INR, and PLT values between positive and negative groups with PCR tests were statistically significant between groups, especially in terms of COVID-19 results.

Coagulopathy becomes evident with increased D-dimer and fibrinogen levels and minimal change in prothrombin time (PT), active partial thromboplastin time (aPTT), and platelet count (15). Hematological laboratory results can be used to determine the severity and prognosis of COVID-19 infection. Thrombocytopenia is associated with an increased risk of severe disease and mortality associated with COVID-19 (18). Platelet count has been accepted as a potential marker for COVID-19 since it is a simple, inexpensive, and readily available hematological marker and since it is independent of disease severity and morbidity risk in the intensive care unit (19).

In a study conducted on thrombocytopenia with patients with COVID-19, mild thrombocytopenia was observed in approximately 5% of patients who had the mild disease; thrombocytopenia was observed in 70-95% of patients who had severe disease (5,19). In a meta-analysis, when platelet count was compared, a significant difference was found between the COVID-19-negative group and the group that had severe COVID-19 in terms of platelet count and the

individuals who had the severe disease were found to have lower platelet count (18). In another study conducted on 1476 patients, a direct correlation was found in patients with COVID-19 between the decrease in platelet count and mortality (20). In another study conducted on patients with COVID-19, it was reported that low platelet count was associated with increased severe disease and death risk, and it could serve as an indicator of worsening of the disease during the hospital stay COVID-19 (18). It has been reported that platelet count decreases significantly in patients with COVID-19 (21,22), and it is lower in patients who do not survive compared with those who survive (23).

Our study was found to be in parallel with the literature, a significant difference was found between groups, and platelet count was found to be lower in the COVID-19 (+) group.

D-dimer is a fragment produced by the cleavage of fibrin by plasmin during clot breakdown (24). One of the most common laboratory findings in patients with COVID-19 who require hospitalization is the apparent elevation in D-dimer. A high D-dimer value has been reported as a poor prognostic marker associated with the consistent critical course and higher mortality in patients with COVID-19 (25,26). In a study conducted on 1099 patients with COVID-19 in China, high D-dimer levels were found in almost half of the patients (27). In an observational study conducted on 183 patients in China, a statistically significant difference was found in the mean D-dimer concentration at admission between patients with COVID-19 who survived and those who did not (8). In another study conducted, patients with COVID-19 treated in ICU (Intensive Care Unit) were found to have higher D-dimer levels than patients with COVID-19 who were not treated in ICU (5). Finally, in another study involving 5279 patients with COVID-19, the COVID-19 (+) group was compared with the COVID-19 (-) group. The D-dimer level of the COVID-19 (+) group was found to be four times higher (28).

Our study was found to be consistent with the literature. The difference between groups was found to be significant. D-dimer levels were found to be higher in the COVID-19 (+) group, while they were found to be lower in the COVID-19 (-) group.

Among coagulation parameters, PT is another laboratory parameter with varying consequences in COVID-19. PT and aPTT are exogenous and endogenous coagulation system factors that can be used to diagnose DIC early (Disseminated Intravascular Coagulation). In another observational study conducted on 183 patients in China, a mild prolongation was found in the mean PT concentration at admission between patients with COVID-19 who survived and those who did not, and a statistically significant difference was found between the groups (8). In another study conducted in China, the patients receiving treatment in the ICU were found to have higher PT prolongation than patients who were not receiving treatment in ICU, and a significant difference was found between the groups (5). In another study conducted on 187 patients diagnosed with COVID-19 and treated in the hospital, patients with high troponin-T levels were found to have prolonged PT and aPTT levels (29). More pronounced PT and APTT parameters prolongation indicates that patients transition from a high coagulation state to a fibrinolytic state due to excessive coagulation factor consumption.

Our study was found to be consistent with the literature; a significant difference was found between the groups in terms of PT levels, and prolongation was found to be higher in the PCR (+) group.

Limitations

There are a number of limitations to this study. First, the research was conducted in a single center. Second, our research was its retrospective design and the data being obtained from files.

In conclusion, the relationship between PT, aPTT, D-dimer, INR, PLT levels were evaluated according to COVID-19 results and gender. Our study showed statistical significance between groups in PT, D-dimer, INR, PLT values between PCR test positive and negative groups in terms of especially COVID-19 results ($p<0.01$). It is crucial to find out coagulopathy and thrombocytopenia in Covid-19 patients. These parameters are also important biomarkers for the prognosis of the disease in COVID-19.

The results of this study have shown that hypercoagulation exists in patients with COVID-19 at an early stage, and hypercoagulation is closely associated with disease progression and clinical outcome. For this reason, coagulation indicators such as D-dimer and PT should be monitored as early as possible to determine thrombotic complications. It is imperative to take preventive treatment to decrease thromboembolism and DIC risk secondary to coagulation disorder and thus to reduce the morbidity and mortality of patients infected with COVID-19.

Conflict of Interest Statement: There is no conflict of interest between the authors.

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