Research Article / Araştırma Makalesi

The Effectiveness of Platelet and D-Dimer Levels in Predicting Prognosis in Intensive Care Patients Diagnosed With COVID-19

COVID-19 Tanılı Yoğun Bakım Hastalarında Prognozu Öngörmede Platelet ve D-Dimer Düzeylerinin Etkinliği

Nuray ALTAY [1], Mahmut Alp KARAHAN [1], Ahmet ATLAS [1]

[1]Department of Anesthesia and Reamination, Faculty of Medicine, University of Harran, Şanlıurfa, TÜRKİYE

Abstract

Background: The pathophysiology of coagulopathy in patients with Corona virus disease 2019 (COVID-19) and its clinical manifestations remain unclear. However, several studies have reported abnormal coagulation parameters, notably in patients with COVID-19 associated pneumonia and acute respiratory distress syndrome. Although the underlying mechanism of COVID-19 coagulopathy remains unknown, it has been suggested to be a form of disseminated intravascular coagulation. We aimed to determine the predictive value of platelet count and D-dimer levels in predicting prognosis in intensive care patients with a diagnosis of COVID-19.
Materials and Methods: Demographic, clinical, laboratory data and radiological findings were obtained from the hospital electronic patient record using a standard data collection form. Platelet counts and D-dimer data were noted. Intensive care stay, mechanical ventilator duration and hospital stay of the patients were analyzed retrospectively. Clinical data covers also comorbid conditions.
Results: The study included 102 intensive care patients with COVID-19 diagnosis. All the patients had Polymerase Chain Reaction (PCR) confirmation and abnormalities on chest computed tomography (CT) consistent with COVID-19. Bilateral pneumonia proven by chest CT was reported in 91.2% of the patient. The platelet count of patients who died was median 247x10^9 /L (min-max 192 - 354), D dimer levels was median 7.03 (min-max 3.36-17.7) mg/L. Patients who living were platelet counts median 310 x10^9/L (min-max 234 – 350), D-dimer levels median 1.59 (min-max 0.82 -2). There was no statistically significant difference when the platelet count of the survived and deceased patients were compared (p=0.193). But the patients who died was D-dimer levels statistically higher (p=0.001).
Conclusions: High or non-decreasing D-dimer levels may indicate poor prognosis in patients with COVID-19 pneumonia whereas platelet counts don't have a predictive value.

Key Words: COVID-19, Intensive Care Unit, D-Dimer, Platelet

Öz

Amaç: Corona Virüs Hastalığı (COVID-19) koagülopatisinin patofizyolojisi ve klinik belirtilerinin altında yatan mekanizma belirsizliğini koruyor. Bununla birlikte, birkaç çalışma, özellikle COVID-19 ile ilişkili pnömoni ve akut solunum sıkıntısı sendromu (ARDS) olan hastalarda anormal pıhtılaşma parametreleri bildirmiştir. COVID-19 koagülopatisinin altında yatan mekanizma bilinmemekle birlikte, bunun bir yaygın damar içi pıhtılaşma (DIC) şekli olduğu öne sürülmüştür. Bu çalışmada, COVID-19 tanılı yoğun bakım hastalarında prognozu öngörmede platelet ve D-dimer düzeylerinin etkinliğini belirlemeyi amaçladık.
Materyal ve Metod: Demografik, klinik, laboratuvar verileri ve radyolojik bulgular, standart bir veri toplama formu kullanılarak hastane elektronik hasta kayıtlarından elde edildi. Platelet sayıları ve D-dimer verileri kaydedildi. Hastaların hastanede kalış süreleri, mekanik ventilatörde kalış süreleri ve yoğun bakımda kalış süreleri retrospektif olarak incelendi.
Bulgular: Çalışmaya COVID-19 tanılı 102 yoğun bakım hastası dahil edildi. Tüm hastalarda Polimeraz Zincir Reaksiyonu(PCR) onayı ve göğüs bilgisayarlı tomografiside (BT) COVID-19 ile uyumlu anormallikler vardı. Göğüs BT ile kanıtlanmış bilateral pnömoni, hastaların %91,2'sinde bildirilmiştir. Ölen hastaların platelet sayısı medyan 247x109 L (min-maks 192 - 354), D dimer seviyesi medyan 7.03 (min-maks 3.36-17.7) mg/L idi. Yaşayan hastalar platelet sayısı medyan 310 x10^9/L (min-maks 234 – 350), D-dimer değerleri medyan 1,59 idi (min-maks 0,82 -2). Yaşayan ve ölen hastaların platelet sayıları karşılaştırıldığında istatistiksel olarak anlamlı bir fark yoktu (p=0.193). Ancak ölen hastaların D-dimer düzeyleri istatistiksel olarak daha yüksekti (p= 0.001).
Sonuç: Yüksek veya azalmayan D-dimer seviyeleri, COVID-19 pnömonisi olan hastalarda kötü prognozu gösterebilirken trombosit sayılarının öngörücü bir değeri yoktur.

Anahtar Kelimeler: COVID-19, Yoğun Bakım Ünitesi, D-Dimer, Platelet

Corresponding Author / Sorumlu Yazar

Dr. Nuray ALTAY
Harran Üniversitesi Tıp Fakültesi Anesteziyoloji ve Reanimasyon Anabilim Dalı,
Osmanbey Kampüsü
Haliliye/Şanlıurfa TÜRKİYE

E-mail: nurayaltay@ymail.com

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Introduction

In early December 2019, a series of cases of pneumonia of unknown etiology emerged in Wuhan City, China. A new enveloped RNA beta-coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been identified as the cause (1). The disease was later named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). WHO declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020 (2,3). Although most patients had a mild clinical course, some patients developed severe pneumonia with a high mortality rate requiring follow-up in intensive care units (ICUs) (3). The mechanism underlying the pathophysiology and clinical manifestations of COVID-19 remains unclear (4). However, it has also been reported that abnormal coagulation parameters are present, especially in patients with COVID-19-associated pneumonia and acute respiratory distress syndrome (ARDS). It has been reported that there are some changes in the hemostatic system and especially increased D-dimer levels are an independent biomarker of poor prognosis in COVID-19 (5). Abnormalities in coagulation parameters have also been reported in these patients. Although the mechanism underlying COVID-19 coagulopathy is unknown, some suggest it is a form of disseminated intravascular coagulation (DIC) (4,5). In the present study, we evaluated the predictive value of platelet and D-dimer levels in predicting the prognosis of COVID-19 intensive care patients.

Materials and Methods

This retrospective case series was approved by our local research ethics committee (Harran University Clinical Research Ethics Committee, date: 23/11/2020 decision number: HRU/20.20.18). Our study included COVID-19 patients admitted to our ICU from May 1, 2020 to July 31, 2020. Chest computed tomography (CT) was performed and oro/nasopharyngeal swab samples for Real time Polymerase Chain Reaction (RT-PCR) were obtained from all suspected patients, in addition to routine blood tests. COVID-19 was diagnosed using consistent clinical manifestations, including fever and respiratory symptoms, findings of pneumonia on CT, and/or positive SARS-CoV-2 PCR results according to WHO interim guidance (1).

The radiological features, clinical and demographic data, and routine blood test results of the patients followed and treated in the intensive care unit were evaluated. Demographic, laboratory data and clinical, radiological findings were obtained from the hospital's electronic patient records using a standard data collection form. Platelet counts and D-dimer data were noted. Intensive care stay, mechanical ventilator duration, and the hospital stay of the patient were analyzed retrospectively.

The COVID-19 treatment protocol in our center comprised pharmacotherapy and respiratory support modalities. Based on the protocol published by the Ministry of Health, pharmacotherapy included antiviral drugs, antibiotics, corticosteroids, and anticoagulants. The patients were administered hydroxychloroquine. Among antiviral drugs, they were prescribed Favipiravir. Corticosteroids (1–2 mg/kg methylprednisolone for 5–7 days) were prescribed to patients with widespread lung infiltration or rapid progression and antibiotics, to those with a secondary bacterial infection. Low-molecular-weight heparin was administered to the patients with high thrombosis risk along with hyperfibrinogenemia.

The criteria for admission to the ICU were as follows: patients with dyspnea, a respiratory rate > 30/min, oxygen saturation below 92%, a PaO_2/FiO_2 ratio < 300, and/or a more than 50% increase in lung infiltration within 24–48 h. Patients without respiratory failure, saturation of 94% with a 2 L/min nasal oxygen, saturation of 92% with room air oxygen, with no need for mechanical ventilation 48 h after extubation, with no need for a vasopressor, and that appeared clinically stable were sent to the ward from the ICU.

Statistical Analysis

The normality of distribution of continuous variables was tested using the Shapiro–Wilk test. The Mann–Whitney U test was used to compare all patients for non-normal data, and the Cohen's d effect size was calculated for numerical variables. Binary logistic regression analysis was performed to estimate the odds ratios and 95% confidence intervals. Receiver operating characteristic (ROC) curve analysis was performed to determinate the diagnostic values of some of the numerical measurements. Statistical analysis was performed with SPSS for Windows version 24.0, and a p value <0.05 was accepted as statistically significant.

Results

The study included 102 ICU patients with a COVID-19 diagnosis. All of the patients had been positive for PCR and abnormalities on chest CT consistent with COVID-19. Patients mean age of the was 69.1 ± 14.3 (24–103) years; 71 patients (69.6%) were male and 31 patients (30.4%) were female. Among the patients, the following conditions were noted: hypertension (HT) in 40 (39.2%) patients, diabetes mellitus (DM) in 28 (27.4%), chronic obstructive pulmonary disease (COPD) in 20 (19.6%), coronary artery disease in 14 (13.7%), heart failure in 4 (3.9%), and cerebrovascular disease in 3 (2.9%). More than one comorbid disease was found in 30 patients (29.4%). The number of patients without comorbid diseases was 19 (18.6%). The most common comorbid disease was HT. Bilateral pneumonia as indicated on chest CT scans was reported in 91.2% of the patients (Table 1), and 80.7% of the patients received mechanical ventilator support. The mean length of stay in the ICU was 8.8 ± 8.9 days, the duration of mechanical ventilation was 5.5 ± 8.8 days, and the mean hospital stay was 12.7 ± 10.5 days (Table 2). All patients received low molecular weight heparin (40–60 mg of enoxaparin/day) and acetylsalicylic acid for 7 days or

longer. Additionally, patients received antiviral and appropriate supportive therapies after admission.

Table 1. Demographic, clinical, and radiologic characteristics of the patients

		Patient (n = 102)
Age (mean ± SD)		69.1 ± 14.3
Sex, n (%)		
Female		31 (30.4)
Male		71 (69.6)
Comorbid disease, n (%)		
DM	Yes	28 (27.5)
	No	74 (72.5)
HT	Yes	40 (39.2)
	No	62 (60.8)
COPD	Yes	20 (19.6)
	No	82 (80.4)
CAD	Yes	14 (13.7)
	No	88 (86.3)
Heart failure	Yes	4 (3.9)
	No	98 (96.1)
CVD	Yes	3 (2.9)
	No	99 (97.1)
CT findings	Bilateral	93 (91.2)
	Unilateral	9 (8.8)

SD: Standard Deviation, DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, CVD: Cerebro Vascular Disease, CT: Computed Tomography

The demographic and hematological parameters of the patients who were discharged from the ICU to the ward (24 patients, 23.5%) and those who died (78 patients, 76.5%) were compared. There was no statistical difference between the two groups in terms of gender or comorbid disease. Mortality was higher in patients of advanced age (median, 72 years), and bilateral infiltration was found by lung CT in all patients who died (p: 0.043, p: 0.004). Among the deceased patients, 37.2% had HT, 29.5% had DM, and 20.5% had COPD (Table 3).

Of the patients who died, the platelet counts were median 247x10^9 L (min-max 192 - 354), and the D dimer levels were median 7.03 (min-max 3.36-17.7) mg/L. Patients who survived COVID-19 were platelet counts 310 × 10^9 L-1 (234–350) and D-dimer values 1.59 (0.82–2) (Table 4). Patients who living were platelet counts median 310 x10^9 L (min-max 234 – 350), D-dimer levels median 1.59 (min-max 0.82 -2). There was no statistically significant difference when the platelet counts of the surviving and deceased patients were compared. However, the D-dimer levels were statistically higher (P =0.001) in those that died. According to the ROC curve analysis, the D-dimer level was successful in predicting mortality in COVID-19 patients. The D-dimer area under the ROC was 0.927 ± 0.03. Accordingly, we observed that the mortality increased in patients with a D-dimer level > 2.01 mg/L.

Table 2. Clinical data of patients

Variables	Non-survivors (n = 78)	Survivors (n = 24)	Cohen d effect size	P
	Median (min–max)	*Median (min–max)*		
ICU stay (days)	6 (3 -13)	5 (3 -9,5)	0,26	0,534
Duration of mechanical ventilation (days)	4 (1 -9)	0 (0 -0)	0,76	***0,001****
Hospital stay (days)	9 (5 -16)	14,5 (9 -18)	0,33	***0,017****

ICU: Intensive Care Unit *Significant at 0.05 level; Median [25%-75%], Mann whitney u test.

Table 3. Relationship of mortality and categorical variables

		Non-survivors (n = 78)	Survivors (n = 24)	OR [95% CI]	*p*
		n (%)	*n (%)*		
CT findings	**Bilateral**	78 (100)	15 (62.5)	46.8 [5.52–397.2]	***0.004****
	Unilateral	0 (0)	9 (37.5)	1 (reference)	
DM		23 (29.5)	5 (20.8)	1.59 [0.53–4.77]	0.409
HT		29 (37.2)	11 (45.8)	1.43 [0.57–3.61]	0.449
COPD		16 (20.5)	4 (16.7)	1.29 [0.39–4.31]	0.679

CT: Computed Tomography, DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease; OR: odds ratio, CI: confidence interval

**Significant at the 0.05 level; univariate binary logistic regression analysis.*

Table 4. Relationship of mortality with clinical and laboratory data

Variables	Exitus (n = 78)	Discharge (n = 24)	Cohen's d effect size	P
	Median (min–max)	*Median (min–max)*		
Age (years)	72 (62–80)	66 (52–75.5)	0.55	***0.043****
Platelet (×10^9 L^{-1})	247 (192–354)	310 (234–350)	0.37	0.193
D-dimer (mg L^{-1})	7.03 (3.36–17.7)	1.59 (0.82–2)	0.78	***0.001****
ICU stay (days)	6 (3–13)	5 (3–9.5)	0.26	0.534
Duration of mechanical ventilation (days)	4 (1–9)	0 (0–0)	0.76	***0.001****
Hospital stay (days)	9 (5–16)	14.5 (9–18)	0.33	***0.017****

*ICU: Intensive Care Unit *Significant at the 0.05 level; median [25%–75%], Mann–Whitney U test.*

Discussion

In this study, 102 COVID-19 positive patients who were followed up in our ICU between May 1, 2020 to July 31, 2020 were included. Our results show that advanced age and D-dimer data were successful in predicting mortality.

The upper respiratory tract forms the entry site for respiratory infections, including SARS-CoV-2 (6). While many patients survived the disease, the prognosis was worse for elderly patients, and elderly patients were considered as the risk group. One study showed an age-related decrease in the clearance of exhaled particles in the small airway region of patients aged 19-81 years, suggesting that this is a relevant factor in the high prevalence of respiratory symptoms among the elderly (7). It is known that there is a gradual decrease in the number of cilia and ciliary cells in the airway with aging in the body. Pulmonary involvement in later stages of respiratory infection can potentially progress to more serious disease, often associated with acute respiratory distress (8). SARS-CoV-2 infection has a wide clinical spectrum, ranging from subclinical symptoms to severe pneumonia. It has been reported that the mean age of the patients followed in the intensive care unit is higher than the patients who do not require intensive care follow-up (9). The median age of surviving patients in this study was reported as fifty-two, and in a similar study, Du et al. found that the median age of non-survivors was 65.8 years (9,10). These data are in line with other studies showing that higher age is associated with a higher risk of COVID-19 mortality (10). Also, some studies have shown that older age is associated with a weakened immune system (11). It has also been reported that COVID-19 disproportionately affects older populations with a significantly higher mortality rate (80% of deaths in patients 65 years and older); among the elderly, approximately 1.3 million live in nursing homes and 1 million live in assisted living shelters. In our study, advanced age was associated with mortality (12). As in previous studies, we attribute this to a weakened immune system and a decrease in ciliary activity with age.

COVID-19 disease has been found to be strongly associated with various coagulopathies (13,14). The pathology may also be consistent with infection-induced inflammatory changes as observed in patients with DIC (15). Due to the limited clinical patient data reported and the lack of available clinical trials data, it is important to explore all possible adjuvant treatments that could contribute to clearer patient outcomes, particularly with regard to the coagulation cascade. It is of particular interest that several circulating inflammatory biomarkers cause coagulation, in particular Fibrinogen, D-dimer, P-selectin, and von Willebrand Factor (VWF). Changes in the levels of these biomarkers are associated with an imbalance between procoagulant and anticoagulant factors. For example, loss of high molecular weight VWF causes bleeding tendencies, while fibrinogen contributes to thrombus formation (16). Coagulation disorders are relatively common in COVID-19 patients, especially those with serious disease (17). Many studies have been published on the relationship of COVID-19 with coagulopathy since the disease first appeared (5, 6). A cohort study of 183 patients found increased prothrombin time (PT) and higher D-dimer and fibrinogen levels in the non-survivor group (18). Similarly, high D-dimer has been reported to be associated with poor prognosis and a fourfold increase in non-survivors (19). Based on the results of our study, we found that non-survivors had a prolonged PT and lower platelet counts; however, multivariate model analysis revealed the association between D-dimer levels and death. This means that early reports on COVID-19 coagulopathy may have overstated the effect of D-dimer as they did not perform a multivariate analysis, and results could be biased by potential confounders. In accordance with this hypothesis, recent publications in which regression analysis was performed have indicated results similar to our own, with hazard ratio values close to 1 for D-dimer (20,21). Zhou et al. in their study in which they examined 191 patients, they found that older age was associated with higher sequential organ failure assessment scores and D-dimer levels. As a result of the study, they predicted that D-dimer levels of 1 mg/mL could help in early identification of patients who may have a poorer prognosis (22). Also, in a similar study, the median standard deviation level of D-dimer in non-survivors was 5.159 (4.679) mg/mL (range, 0.27-26 mg/mL) and 70.6% of patients had a D-dimer level of 1 mg/mL has been reported (10). In a multicenter retrospective study conducted in the early stages of the COVID-19 outbreak, it was reported that 46.4% of patients with COVID-19 infection had high D-dimer levels (≥ 0.5 mg/L), and the elevation increased with severity of the disease (23). Thus, D-dimer variability may reflect disease severity, and an increased level is associated with adverse outcomes in patients with community-acquired pneumonia (24). In a study of 99 cases of COVID-19 in Wuhan, China, elevated D-dimer levels (> 1.5 mg/L) were detected in 36% of patients (25). In another retrospective study conducted in China and including 41 patients, it was shown that D-dimer and PT levels were higher at admission in patients requiring ICU support (median D-dimer level, 2.4 mg/L for ICU vs. 0.5 mg/L for non-ICU patients, P = 0 .004; median PT, 12.2 s for ICU patients vs. 10.7 s. (26). Similarly, Wang et al. also reported that D-dimer levels were significantly higher in patients requiring intensive care treatment compared to less severe cases (27). In another study of 201 patients with COVID-19 pneumonia, increased PT was associated with ARDS risk, while increased D-dimer levels were also significantly associated with ARDS and death (P < 0.001) (28). Elevated D-dimer levels (>1 mg/mL) were also shown in another multicenter retrospective study to be significantly associated with in-hospital deaths (17). Interestingly, D-dimer levels among non-survivors showed a sequential increase over time compared with survivors (17, 27 In a prospective study examining the coagulation profile in COVID-19 patients, D-dimer, fibrin/fibrinogen degradation product (FDP) and fibrinogen levels were significantly higher among patients for all three

comparisons compared to healthy controls. Patients with poor clinical manifestations showed higher D-dimer and FDP values than those with milder symptoms (29). All these studies mentioned above show that D-dimer elevation and DIC may be common in patients with a severe COVID-19 infection (30). Endothelial dysfunction and immune dysregulation may be the main issues in explaining the underlying pathophysiology in future studies (31). Our findings show that D-dimer levels will able to predict the disease prognosis of COVID-19.

Du et al. found that 58 (68.2%) of the 85 patients they examined had one or more comorbidities (10). In line with other studies, they reported the most common comorbidities affecting mortality in COVID-19 patients as follows; Hypertension (32 [37.6%]), diabetes (19 [22.4%]), and coronary heart disease (10 [11.8%]) (32). Similar to the results obtained in previous studies, HT and diabetes were the most common comorbidities in COVID-19 patients (25-27). In our study, HT was the most common comorbid disease in our patients.

In summary, most of our COVID-19 patients who died were in men over 60 with chronic diseases such as HT, diabetes and coronary heart disease. High or non-decreasing D-dimer levels may indicate a poor prognosis for COVID-19.

Conclusion

Elevated levels of D-dimer were associated with worse outcomes among COVID-19 patients in ICU. In hospitalized COVID-19 patients, this parameter should be closely monitored. Morbidity and mortality can be prevented with early interventions by evaluating D-dimer levels.

Ethical Approval: This retrospective case series was approved by our local research ethics committee (Harran University Clinical Research Ethics Committee, date: 23/11/2020 decision number: HRU/20.20.18).

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