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Procalcitonin is a predictor of disseminated intravascular coagulation in patients with fatal COVID-19

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Abstract. – OBJECTIVE: The coagulopathies that present with COVID-19 are thrombotic microangiopathy and disseminated intravascular coagulopathy (DIC). Procalcitonin (PCT) levels have been shown to be significantly increased in COVID-19 patients in comparison with healthy subjects/asymptomatic coronavirus-positive patients. In this report, our aim was to assess the associations of the PCT level with DIC and the severity of COVID-19 infection.

PATIENTS AND METHODS: In this cross-sectional, retrospective study, 71 consecutive patients with severe COVID-19 (21 with DIC and 50 without DIC) were enrolled in the study. The PCT level was obtained from hospital records.

RESULTS: The PCT level was significantly higher in the patients with DIC than in those without DIC [1.9 (0.6-14.5) *vs.* 0.3 (0.2-0.4) (ng/mL), $p<0.01$]. The PCT level showed a positive and significant correlation with DIC ($r=0.382$, $p=0.001$) and was an independent predictor of DIC in patients with severe COVID-19 (OR: 6.685, CI: 1.857-24.063, $p<0.01$).

CONCLUSIONS: In summary, the PCT level was increased in severe COVID-19 patients with DIC compared with those without DIC. An increased PCT level might suggest the presence of DIC and may help in predicting COVID-19 severity.

Key Words:
COVID-19, Disseminated intravascular coagulopathy, Procalcitonin, D-dimer, Prothrombin time.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), which causes Coronavirus disease 2019 (COVID-19), progressed from an epidemic in Wuhan, China, into a global pandemic[1]. Although COVID-19 causes primarily upper respiratory tract infections, over the initial months, the clinical outcomes/manifestations have changed drastically. There have been increasing numbers of severe cases with systemic abnormalities, including organ dysfunction, thrombosis, and even death[2,3]. Coagulopathy, which is common in COVID-19 patients, is one of the most adverse prognostic signs of severe COVID-19 infection and is associated with increased mortality[4,5]. COVID-19-associated coagulopathy consists of thrombotic microangiopathy and disseminated intravascular coagulopathy (DIC), which affects bodily function in severe cases. Some of the most common coagulopathic findings in these patients are an increased D-dimer level, reduced platelet count, and sustained prothrombin time (PT). The International Society on Thrombosis and Hemostasis (ISTH) supports D-dimer, platelet count, and PT assessments in COVID-19 patients.

DIC is associated with the formation of systemic fibrin, which results from increased thrombin expression, concomitant physiological anticoagulant suppression, and dysfunctional fibrinolysis[6]. Reduced platelet counts, sustained PT, and increased D-dimer levels are diagnostic of DIC in sepsis[7]. DIC development was reported a median of 4 days (range, 1-12 days) after hospital admission in COVID-19 patients[5]. Wu et al[8] evaluated acute respiratory disease syndrome (ARDS) related factors in COVID-19 patients and suggested that DIC-associated difficulties may contribute to death independently from ARDS. Tang et al[5] reported more frequent deterioration of coagulation parameters in severe COVID-19 patients. They also confirmed DIC in 71.4% of severe COVID-19 patients and 0.6% of asymptomatic subjects.

Procalcitonin (PCT), the precursor of calcitonin, is generally expressed and secreted by thyroid parafollicular C cells. However, it is also

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induced by bacterial infections in extrathyroidal tissues[9]. PCT has been shown to be induced by bacterial and viral infections differentially and has been used to distinguish these infections[11]. In healthy subjects, circulating PCT is generally undetectable[10]. Higher PCT levels in critical COVID-19 patients may be suggestive of a bacterial infection, which complicates the course of COVID-19. PCT levels were found to be increased in critical compared with severe COVID-19 patients[4]. In a retrospective cohort of 191 COVID-19 patients[12], the fatal cases had higher PCT and interleukin-6 levels compared with the non-fatal cases. Moreover, a meta-analysis (of four studies)[13] demonstrated that an increased PCT level was independently linked to severe COVID-19 infection.

The objective of this study was to assess the link between PCT and DIC in fatal COVID-19 cases and to determine whether the PCT level predicts the development of DIC in these cases.

Patients and Methods

The study used a cross-sectional, observational design. From April 2020 to June 2020, a total of 71 consecutive fatal COVID-19, 21 with DIC [DIC (+)] and 50 without DIC [DIC (–)] patients were admitted to the ICU and enrolled in the study. Real-Time Reverse-Transcription Polymerase Chain Reaction (RT-PCR) was performed on nasal swabs from these patients who complained of COVID-19-related symptoms, including cough, fever, shortness of breath, gastrointestinal illness, or fatigue, or who had clinician concerns or known exposure to a coronavirus-positive patient. According to the WHO, the diagnosis of COVID-19 was determined using RT-PCR. Critical illness was defined as those who needed admittance to the ICU, needed mechanical ventilation, or died. Severe status was defined by the following: respiratory distress, respiratory rate $\geq$ 30 times/minute, below resting state, oxygen saturation $\leq$ 93%, and oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) in arterial blood $\leq$ 300 mmHg.

Electronic health records were used to obtain information on age, sex, medical history (e.g., hypertension, diabetes mellitus, atrial fibrillation, chronic kidney disease, or coronary artery disease), and any previous pulmonary disease. We also obtained information on current medication usage and in-hospital complications (e.g., ARDS, pneumonia, acute kidney failure, myocardial injury, pulmonary embolism, and multiple organ dysfunction scores). Scoring for compensated and overt DIC endorsed by the ISTH should be used for DIC detection[14].

Serological specimens were obtained on admission and sent to the laboratory for analysis. Blood was collected in EDTA tubes and analyzed using an automatic blood counter. Hematological factors were examined using the LH 780 analyzer (Beckman Coulter, Inc., Brea, CA, USA). Glucose, creatinine, sodium, potassium, and CRP levels were measured using commercial kits on the Architect c8000 Chemistry System (Abbott Diagnostics, Wiesbaden, Germany). Troponin I and D-dimer levels were evaluated using an immunoassay analyzer (AQT90 FLEX; Radiometer, Copenhagen, Denmark). The PCT level was measured using the Roche electrochemiluminescence method. The study was approved by the Internal Review Board of our center and was performed under the Ethical Standards of the Declaration of Helsinki.

Statistical Analysis

Data were examined using SPSS software v25.0 for Windows (Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the presence of a normal distribution of the continuous variables. Variables with a normal distribution are expressed as means ± standard deviation, whereas those with a non-normal distribution are expressed as medians with interquartile ranges. Categorical variables are expressed as percentages. Group differences were assessed using Student's unpaired *t*-test or the Mann-Whitney U test. The frequencies of nominal variables were compared using Fisher's exact test or the Chi-square test. Pearson's and Spearman's tests were used for correlation analyses. Multivariate logistic regression was used to determine independent predictors of DIC. A p-value < 0.05 was considered significant.

Results

The clinical and demographic characteristics of the 71 fatal COVID-19 cases are shown in Table I. No significant differences were found between groups in terms of age, sex, or hospital stay length. The medical histories of the patients and prior drug use were similar between the two groups. In-hospital multiple organ dysfunction syndromes were more common in the DIC (+) group compared with the DIC (–) group ($p <$

Table I. The demographic and clinical data of the study population.

	Total (n=71)	DIC (-) (n=50)	DIC (+) (n=21)	*p*-value
Age. years	69.3±11.4	69.4±11.1	68.5±12.1	0.51
Gender; male, n (%)	37 (52)	28 (56)	11 (55)	0.78
Hospitalization, days	11 (1-28)	11 (6-15)	11 (3-18)	0.57
Previous medical history				
Diabetes mellitus, n (%)	28 (40)	21 (42)	7 (33)	0.49
Hypertension, n (%)	43 (60)	33 (66)	10 (48)	0.14
Coronary artery disease, n (%)	21 (30)	16 (32)	5 (24)	0.49
Atrial fibrillation, n (%)	5 (7)	4 (8)	1 (5)	0.62
COPD, n (%)	12 (17)	8 (16)	4 (9)	0.75
Chronic kidney failure, n (%)	8 (11)	6 (12)	2 (10)	0.76
Medication				
Beta-blocker, n (%)	23 (32)	18 (36)	5 (24)	0.32
ACE inhibitor, n (%)	16 (22)	11 (22)	5 (24)	0.86
ARB, n (%)	15 (21)	13 (26)	2 (10)	0.12
CCB, n (%)	23 (32)	17 (34)	6 (29)	0.65
Acetylsalicylic acid, n (%)	18 (25)	13 (26)	5 (24)	0.84
Oral antidiabetic, n (%)	27 (38)	20 (40)	7 (33)	0.59
Insulin, n (%)	9 (13)	8 (16)	1 (5)	0.19
In hospital complications				
ARDS, n (%)	61 (86)	41 (82)	20 (95)	0.14
Pneumonia, n (%)	60 (84)	43 (86)	17 (81)	0.59
Acute kidney failure, n (%)	23 (32)	12 (24)	11 (52)	0.02
Myocardial injury, n (%)	26 (37)	16 (32)	10 (48)	0.21
Pulmonary embolism, n (%)	5 (7)	-	5 (24)	
MODS, n (%)	21 (30)	10 (20)	11 (52)	<0.01

DIC, Disseminated intravascular coagulation; COPD, Chronic obstructive pulmonary disease; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; ARDS, Acute respiratory disease syndrome. MODS, Multiple organ dysfunction syndrome.

0.01). Pulmonary embolism was observed in five patients in the DIC (+) group. No differences were observed in the rate of ARDS, acute kidney failure, or myocardial injury between groups.

The biochemical and hematological parameters of the patients are shown in Table II. The PCT level was significantly increased in the DIC (+) group compared with the DIC (−) group [1.9 (0.6-14.5) *vs.* 0.3 (0.2-0.4) (ng/mL), $p < 0.01$] (Figure 1). Moreover, DIC (+) patients had a higher CRP level compared with DIC (−) patients [188 (112-250) *vs.* 101 (63-166) (mg/L), $p < 0.01$]. Other biochemical parameters were similar between the groups. The white blood cell count was higher, and the hemoglobin level lower in the DIC (+) group compared with the DIC (−) group. The neutrophil count was similar between the groups, whereas the lymphocyte count was lower in the DIC (+) group compared with the DIC (−) group. DIC (+) patients had higher platelet levels, and a longer activated partial thromboplastin time (APTT) compared with DIC (−) patients. However, the PT and international normalized ratio were similar between the groups. Although no difference in the D-dimer level was found between the groups, the DIC (+) patients had a higher fibrinogen level than that in the DIC (−) patients.

Table III presents the correlations between the PCT level and clinical parameters. There was an inverse correlation between the PCT level and platelet count ($r = -0.265$, $p = 0.03$). Moreover, the PCT level was positively and significantly correlated with DIC ($r = 0.382$, $p = 0.001$). Multivariate logistic regression analyses of the associations between DIC and multiple parameters are shown in Table IV. PCT (OR: 6.685, CI: 1.857-24.063, $p < 0.01$) was found to be an independent predictor of DIC in fatal COVID-19 cases.

Discussion

We found higher PCT levels in fatal COVID-19 cases with DIC (+) compared with severe COVID-19 cases without DIC. A significant positive correlation was found between the PCT level and DIC, and PCT was an independent predictor of DIC, in the fatal COVID-19 cases.

Table II. Laboratory parameters of study population.

	Total (n=71)	DIC (-) (n=50)	DIC (+) (n=21)	*p*-value
Biochemical				
Sodium (mEq/L)	141.6±10.1	137 (134-144)	141 (138-151)	0.05
Potassium (mEq/L)	4.2±0.8	4.2 (3.8-4.7)	3.9 (3.4-4.8)	0.20
Serum glucose (mg/dl)	142 (109-237)	130.5 (111.3-182.8)	199 (87-313)	0.07
Urea (mg/dl)	61 (40-112)	58 (37-106)	80 (52-148)	0.08
Creatine (mg/dl)	1.1 (0.7-1.8)	1.1 (0.7-1.7)	1.6 (0.8-2.3)	0.16
C-reactive protein (mg/L)	113 (69-210)	101 (63-166)	188 (112-250)	<0.01
Procalcitonin (ng/mL)	0.4 (0.2-1.2)	0.3 (0.2-0.4)	1.9 (0.6-14.5)	<0.01
Creatine kinase MB (ng/mL)	2.7 (1.4-7.3)	2.6 (1.1-5.6)	4 (2-15)	0.11
Troponin (ng/mL)	78 (40-280)	97 (46-351)	65 (30-115)	0.21
Hematologic				
WBC (10^3/µL)	7.7 (5.4-12.0)	7.9 (5.7-13.0)	16.8 (12.9-20.8)	<0.01
Hemoglobin (g/dL)	11.1±2.3	11.7 (10.4-13.3)	9 (8-11)	<0.01
Neutrophil. 10^3/µL	6.3 (4.1-10.9)	6.5 (4.3-11.1)	5.9 (2.1-9.8)	0.29
Lymphocyte. 10^3/µL	0.9 (0.5-1.2)	0.9 (0.7-1.3)	0.5 (0.2-1.1)	<0.01
Platelet (10^3/µL)	149 (100-231)	201 (125-240)	86 (15-137)	<0.01
Prothrombin time (sec)	13.5±2.5	13 (12-14)	14 (12-16)	0.06
aPTT (sec)	29 (26-34)	28 (25-30)	35 (28-49)	<0.01
INR (mg/L)	1.3 (1.1-1.4)	1.3 (1.1-1.4)	1.3 (1.2-1.6)	0.06
D-Dimer (ng/mL)	3220 (1820-4760)	2580 (1824-4202)	4570 (1710-5500)	0.12
Fibrinogen	271±46	258±40	300±50	0.01

DIC, Disseminated intravascular coagulation; WBC, White blood cell count; aPTT, activated partial thromboplastin time; INR, International normalized ratio.

Abnormalities in coagulation parameters are generally observed in severe COVID-19 infection, with a higher D-dimer level being the most frequently observed[15]. Coagulation abnormalities are linked to a higher mortality rate of severe COVID-19[16]. Generally, COVID-19-associated coagulation disorders are characterized by low-grade DIC and pulmonary thrombotic microangiopathy[17]. Tang et al[5] evaluated the coagulation parameters of 183 patients with novel coronavirus pneumonia; patients with fatal COVID-19 had higher levels of D-dimers and fibrin degradation products and prolonged PT and APTT upon admittance compared with those with non-fatal COVID-19 ($p < 0.05$). Those authors also showed that increased D-dimer and fibrin degradation product levels are common in patients with fatal COVID-19. These findings suggest the presence of a common coagulation activation pathway and secondary hyperfibrinolysis condition in patients with fatal COVID-19[5]. Zhou et al[12] showed that COVID-19 patients with an increased D-dimer level (> 1 mg/L) at admission to the hospital had an 18-fold greater risk of mortality (95% CI 2.6-128.6; $p = 0.0033$). Furthermore, increased PT and D-dimer levels have been linked to ARDS in COVID-19 cases. Some authors reported simi-

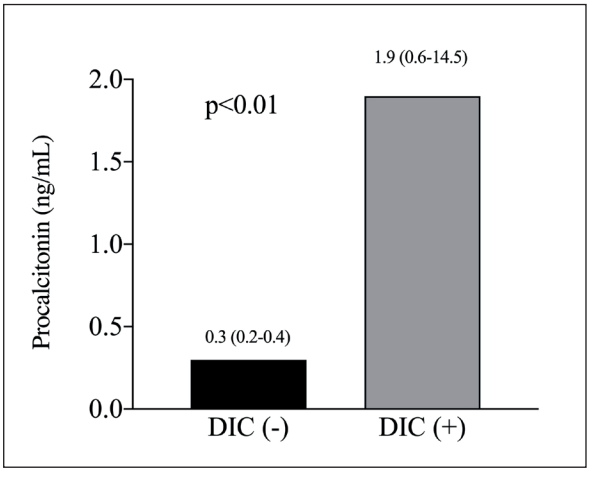

Figure 1. Meta-analysis of treatment withdrawal for alginate + PPI *vs.* PPI.

Table III. Correlation between the procalcitonin and clinical parameters.

	p	*r*
Platelet	0.03	-0.265
D-Dimer	0.25	0.137
Prothrombin time	0.40	0.101
International normalized ratio	0.44	0.094
Disseminated intravascular coagulation	0.001	0.382

Table IV. Multivariate logistic regression analyses of disseminated intravascular coagulation.

	p-value	Odds ratio	95%CI	
			Lower	Upper
C-reactive protein	0.32	0.995	0.985	1.005
Troponin I	0.45	1.000	0.999	1.001
Procalcitonin	<0.01	6.685	1.857	24.063
Diabetes mellitus	0.99	0.988	0.202	4.837
Hypertension	0.56	1.617	0.327	8.001

lar platelet counts at admission between severe and non-severe COVID-19 patients[8,16]. In this study, we reported higher platelet counts at hospital admission in fatal DIC (+) compared with fatal DIC (−) cases.

Sepsis, a common cause of DIC, may be linked to viral infections. In viral infections, an antigen-antibody complex is formed, resulting in generalized endothelial capillary infection, septic coagulopathy, uncontrolled release of pro-inflammatory cytokines, widespread activation of the blood coagulation system, and DIC development. It was reported[18] that 2.5% of SARS patients had DIC complications, which were often associated with mortality. COVID-19 infection worsens DIC complications[5,19]. Moreover, patients with fatal COVID-19 generally have been documented to have DIC complications. A previous study[5] found that 71.4% of fatal and 0.6% of non-fatal patients with COVID-19-related pneumonia developed DIC during their hospital stay. On the other hand, Deng et al[15] reported that 6.4% of COVID-19 patients had DIC.

The circulating PCT level is generally normal in patients with viral infections, whereas an increased level generally suggests a bacterial superinfection[20]. PCT can be used to differentiate bacterial and viral infections. Higher PCT levels in critical patients are suggestive of a bacterial infection concurrent with severe COVID-19.

Generally, patients with mild COVID-19, compared with severe COVID-19, have lower PCT levels[21]. Lippi and Plebani[13] reported that increased PCT levels were associated with severe COVID-19 infection. Liu et al[22] evaluated 141 COVID-19 patients retrospectively and reported increased PCT levels (> 0.07 ng/mL) at hospital admission in those with severe compared with mild COVID-19. Zhou et al[23] demonstrated significantly higher PCT levels in patients with critical compared with severe COVID-19. Furthermore, Guan et al[4] showed that PCT and CRP were significantly increased in severe COVID-19 compared to non-severe infections. Those authors also proposed that increased PCT levels were associated with ICU admission, need for mechanical ventilation, and mortality. Wang et al[16] evaluated 138 COVID-19 patients reported a threefold greater risk of hospitalization in the ICU in patients with higher versus lower PCT levels (75% *vs*. 22%; $p < 0.001$). Moreover, Lippi et al[13] showed that an advanced surge in PCT expression may be a predictor of worse outcomes.

In this study, fatal COVID-19 patients with DIC presented with higher PCT and CRP levels compared with those without DIC. The increased PCT level may be associated with a concurrent bacterial infection in these patients. Therefore, antibiotic therapy should be considered in COVID-19 patients with higher PCT levels and white blood cell counts. We also speculated that bacterial superinfection might contribute to DIC positivity in patients with severe COVID-19.

Administration of prophylactic doses of low-molecular-weight heparin (LMWH) is the only treatment for COVID-19-associated microangiopathy. Heparin or LMWH therapy reduces the mortality rate of severe COVID-19. All severe COVID-19 cases are treated with LMWH unless there is a contraindication (active bleeding, platelet count < 25,000, intolerance to LMWH). It has been shown that LMWH therapy significantly reduces the COVID-19-related mortality rate in severe patients with DIC (+) and high D-dimer levels. Furthermore, COVID-19 patients with elevated D-dimer levels had lower mortality rates after receiving heparin compared with no heparin[24].

Limitations

This study was limited by the relatively small number of patients, which was due to the single-center study design. The relatively small number of patients might have decreased the strength of the results and conclusions obtained from this

study. Furthermore, because our patients included only those with fatal COVID-19 infections, our findings cannot be generalized to patients who survive COVID-19. Another limitation was the lack of data on fibrin degradation product levels, which are not measured in our hospital. Despite these limitations, our study provides significant results to aid future studies on PCT levels in fatal COVID-19 cases.

Conclusions

In summary, we found increased PCT levels in severe COVID-19 DIC (+) compared with DIC (−) cases. Further, we demonstrated that a higher PCT level might suggest DIC positivity and help predict the severity of COVID-19. Early diagnosis of DIC and identification of a higher PCT level might guide therapy in severe COVID-19 patients.

Conflict of Interests

This study received no grant from any funding agency in the public, commercial or not-for-profit sectors. The authors report no conflicts of interest.

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