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Research Article

Evaluation of coagulation parameters according to serum CRP levels in early stage COVID-19 patients

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Abstract

Objectives: An increase in the levels of inflammatory biomarkers is observed in coronavirus disease (COVID-19). Coagulopathy occurring during the course of the disease has also been associated with inflammation. In our study, we aimed to evaluate the coagulation parameters according to the severity of inflammation in patients with early stage COVID-19 disease.

Methods: The study was carried out retrospectively in a third-level hospital between April 8 and August 20, 2020. The patients were divided into two groups according to polymerase chain reaction (PCR) results. Non-COVID-19 group consisted of 72 patients with negative, and COVID-19 group consisted of 247 patients with positive PCR results. According to the serum C-reactive protein (CRP) levels the COVID-19 patients were divided into three groups as follows: Group1 (CRP<10 mg/L; n=105), Group 2 (CRP 10-50 mg/L; n=72), and Group 3 (CRP >50 mg/L; n=70). Age, CRP, and coagulation parameters including fibrinogen, D-dimer, aPTT, and PT were compared between the groups.

Results: There were significant differences between the non-COVID-19 and COVID-19 patients in terms of age, CRP and coagulation parameters. Likewise, there was a significant difference among 3 groups regarding coagulation parameters. In the multinomial logistic regression analysis, only level of D-dimer was an independent risk factor among all groups, while PT was an independent risk factor between Groups 1, and 3.

Conclusion: Our findings suggest that coagulopathy occurs in the early stage in relation to the severity of inflammation. For the diagnosis of COVID-19 disease and the detection of thrombotic complications; it is important to monitor results of the coagulation tests along with markers of inflammation from the early stages of the disease.

Keywords: Coagulation, COVID-19, C-reactive protein, inflammation

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In December 2019 World Health Organization (WHO) announced the cases of a fatal coronavirus disease (COVID-19), in Wuhan Province of Public Republic of China which heralded the emergence of a worldwide pandemic [1]. The systemic inflammatory response seen in COVID-19 is an important feature of the disease. Many authors have demonstrated higher levels of biomarkers such as fibrinogen and C-reactive protein (CRP) in patients with COVID-19 [1, 2]. A relationship has been demonstrated between acute phase reactants CRP, and the severity of COVID-19 disease [3, 4].

The main adverse effect of the disease is lung damage [5]. Despite favorable prognosis observed in most patients, rapid progression of the disease to respiratory distress syndrome, coagulopathy, and multiple organ failure has been noted in some

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patients [6]. An over activated immune system causes widespread tissue damage and prothrombotic complications [7].

Many researchers have explained the resulting coagulopathy through inflammatory processes [2, 8]. All pro-inflammatory cytokines including IL-6, IL-1β, tumor necrosis factor-alpha, and complement system proteins can induce coagulopathy [9] which is termed by some experts as thromboinflammation or COVID-19-associated coagulopathy [10].

Many studies have indicated that high D-dimer and fibrinogen levels are prognostic risk factors for the disease [2, 8, 10, 11].

Inflammation and coagulopathy are the main defense mechanisms against the disease, which aggravate in proportion to the severity of the disease [12].

For the diagnosis of COVID-19 disease and the detection of thrombotic complications; it is important to monitor coagulation tests along with markers of inflammation from the early stages of the disease.

In our study, we aimed to evaluate coagulation parameters according to the severity of inflammation in early stage COVID-19 patients.

Materials and Methods

Study population

The study was carried out retrospectively between 8 April and 20 August 2020 in the 1st months of the pandemic in our country. A total of 319 patients over the age of 18 who applied to the University of Health Sciences Tepecik Training and Research Hospital Emergency Department and pandemic outpatient clinic were included in the study. Patients using an oral anticoagulant were excluded from the study.

Polymerase chain reaction (PCR) test was applied to all patients, and the patients with positive and negative PCR test results were allocated to COVID-19 (n=247), and non-COVID-19 (n=72) groups, respectively.

COVID-19 patients were also divided into three groups based on their blood CRP levels as follows: Group 1: CRP <10 mg/L (n=105), Group 2: CRP 10–50 mg/L (n=72), and Group 3: CRP >50 mg/L (n=70). This classification was adapted according to the meta-analyses in the literature and the COVID-19 Guide of the Turkish Ministry of Health [13, 14].

Clinical signs, symptoms, comorbidities, and coagulation parameters were compared among these groups.

Biochemical analysis

Results of CRP (0–5 mg/L), D-dimer (0–500 µg/L), fibrinogen (170–420 mg/dl), prothrombin time (PT, 10.8–15 s), and activated partial thromboplastin time (aPTT) (21–36 s) with indicated reference ranges in parentheses recorded at the time of admission were collected retrospectively. Serum CRP levels were measured in the AU 5800 autoanalyzer (Beckman Coulter Inc., USA); values of D-dimer, fibrinogen, PT, and aPTT were determined using a coagulation analyzer (Sysmex CS-2500, Siemens, USA).

Statistical analysis

SPSS 23.0 (IBM SPSS Statistics v.23) program was used for statistical analysis. Continuous variables were expressed as mean±standard deviation or as median (25–75th percentile), and categorical variables as numbers (n), and percentages (%). The normality of the distributions of the variables was evaluated with the Kolmogorov–Smirnov test. Independent t-test and Mann–Whitney U test were used in the comparison of two independent variables. One-way analysis of variance (ANOVA) was used for the comparison between groups with normally distributed data, and Kruskal–Wallis test for non-normally distributed data. Tukey test and Games-Howell test were used for pairwise comparisons based on the results of ANOVA test.

Mann–Whitney U test was used in paired groups of statistically significant parameters. The level of significance with Bonferroni correction was set as 0.05/3=0.017t. Chi-square test and Fisher's exact test were used to compare categorical variables between groups. Spearman correlation analysis was performed to assess correlations between parameters. To determine the prognostic predictive value of coagulation parameters in COVID-19 patients, multinomial logistic regression analysis was performed by considering the Group 1 as the reference group. P<0.05 was considered statistically significant.

Results

Symptoms and comorbidities seen in COVID-19 patients are shown in Tables 1 and 2.

The most frequently seen comorbidities in COVID-19 patients were diabetes mellitus (12.9%) and cerebrovascular disease (9.3%). A statistically significant difference was observed between groups in terms of malignancy (p<0.001) (Table 2).

Significant differences were found between the COVID-19 and non-COVID-19 patients as for CRP (p<0.001), fibrinogen (p=0.002), D-dimer (p<0.001), aPTT (p<0.001), and PT (p=0.024) parameters (Table 3).

Values of coagulation parameters of COVID-19 patients grouped according to CRP values are given in Table 4. aPTT values differed only between Groups 1, and 2 (p=0.008).

In COVID-19 patients, a positive correlation was observed between serum CRP levels, and parameters of age (r=0.518, p<0.001), D-dimer (r=0.622, p<0.001), fibrinogen (r=0.606, p<0.001), and PT (r=0.280, p<0.001), while a negative correlation existed between serum CRP levels and aPTT (r=–0.300, p<0.001).

According to the multinomial logistic regression analysis, only D-dimer level was found to be an independent risk factor. In addition, PT was an independent risk factor between Groups 1 and 3 (Table 5).

Discussion

COVID-19 infection is associated with coagulation abnormalities characterized by increases in levels of procoagulant factors such as fibrinogen and D-dimer. In our study, we examined

Table 1. Symptoms seen in COVID-19 patients

	COVID-19 n=247		Group 1 CRP<10 mg/L n=105		Group 2 CRP 10–50 mg/L n=72		Group 3 CRP >50 mg/L n=70		p
	n	%	n	%	n	%	n	%	
Male		48.9		46.6		44.4		55.5	0.307
Asymptomatic	20	8.1	16	80	2	10	2	10	0.001*
Fever	53	21.4	15	28.3	18	34	20	37.7	0.162
Weakness	104	42.1	29	27.9	37	35.6	38	36.5	0.006*
Headache	35	14.2	23	65.7	8	22.9	4	11.4	0.002*
Sore throat	34	13.7	14	41.2	9	26.5	11	32.4	0.943
Back pain	17	6.9	6	35.3	6	35.3	5	29.4	0.814
Chest pain	9	3.6	5	55.6	2	22.2	2	22.2	0.691
Cough	80	32.3	35	43.8	27	33.8	18	22.5	0.084
Shortness of breath	53	21.5	17	32.1	17	32.1	19	35.8	0.395
Myalgia	34	13.8	10	29.4	8	23.5	16	47.1	0.098
Anosmia	24	9.7	8	33.3	8	33.3	8	33.3	0.761
Loss of taste	23	9.3	4	17.4	4	17.4	15	65.2	0.001*
Nausea/vomiting	12	4.8	3	25	4	33.3	5	41.7	0.538
Palpitation	7	2.8	1	14.3	1	14.3	5	71.4	0.086
Diarrhea	15	6.1	6	40	7	46.7	2	13.3	0.174
Abdominal pain	6	2.4	0	0	1	16.7	5	83.3	0.017*

*: Statistically significant parameters. CRP: C-reactive protein

Table 2: Comorbidities of COVID-19 patients

	COVID-19 n=247		Group 1 CRP<10 mg/L n=105		Group 2 CRP 10–50 mg/L n=72		Group 3 CRP >50 mg/L n=70		p
	n	%	n	%	n	%	n	%	
CHF	6	2.4	1	16.7	3	50	2	33.3	0.381
CAD	18	7.2	3	16.7	6	33.3	9	50	0.063
HT	20	8.1	5	25	6	30	9	45	0.268
COPD	10	4	3	30	4	40	3	30	0.664
CVD	23	9.3	4	17.4	7	30.4	12	52.2	0.025
Malignity	19	7.7	2	10.5	3	15.8	14	73.7	<0.001*
Asthma	10	4	3	30	2	20	5	50	0.505
Thyroid Disease	8	3.2	4	50	3	37.5	1	12.5	0.602
Migraine	4	1.6	2	50	0	0	2	50	0.562
Embolism	3	1.2	1	33.3	0	0	2	66.7	0.492
DM	32	12.9	7	21.9	9	28.1	16	50	0.023
MR	4	1.6	2	50	2	50	0	0	0.471

*Statistically significant parameters. CHF: Congestive heart failure; CAD: Coronary artery disease; HT: Hypertension; COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; DM: Diabetes mellitus; MR: Mitral regurgitation.

CRP levels and coagulation parameters in COVID-19 patients, and found a significant increase in fibrinogen, D-dimer and PT levels, and a significant shortening in aPTT. These findings are consistent with the results of previously reported similarly designed studies [15–17].

In our study, we observed significant intergroup differences in terms of fibrinogen and D-dimer levels which increased in proportion to the severity of inflammation in the patient groups constructed according to CRP values. Similar results compatible with our findings have been reported in other studies [18, 19].

Table 3. Coagulation parameters of non-COVID-19 and COVID-19 patients

	non-COVID-19 n=72	COVID-19 n=247	p
Male %	59.7	48.9	0.091
Age	34±9	52±17	<0.001*
CRP (mg/L)	1.4 (0.7–2.8)	18.1 (5.47–74.3)	<0.001*
Fibrinogen (mg/dL)	279 (241–322)	355 (292–404)	0.002*
D-dimer (µg/L)	190 (190–260)	540 (290–920)	<0.001*
aPTT (s)	26.58±1.6	24.32±2.52	<0.001*
PT (s)	11.68±0.79	12.35±1.26	0.024*

*: Statistically significant parameters (p<0.05). CRP: C-reactive protein; aPTT: activated partial thromboplastin time; PT: Prothrombin time.

Tablo 4. Coagulation parameters of COVID-19 patients

	Group 1 CRP<10 mg/L n=105	Group 2 CRP 10–50 mg/L n=72	Group 3 CRP >50 mg/L n=70	p
Age	42±14	54±14	58±15	<0.001*
CRP (mg/L)	3.8 (1.7–6.6)	21.3 (14.2–31.5)	98.05 (70.8–125.1)	<0.001*
Fibrinogen (mg/dL)	320 (275–370)[a*,b*]	379 (341–434)[c*]	561 (456–757)	<0.001*
D-dimer (µg/L)	290 (190–492)[a*,b*]	550 (355–895)[c*]	780 (570–1152)	<0.001*
aPTT (s)	24.70±2.1[a*]	23.60±2.4	24.2±2.7	0.017*
PT (s)	12.01±0.71[b*]	12.02±0.64[c*]	12.80±1.55	<0.001*

*: Statistically significant parameters (p<0.05). [a]: Statistically significant correlation between the Groups 1 and 2 (p<0.05); [b]: Statistically significant correlation between Groups 1 and 3 (p<0.05); [c]: Statistically significant correlation between Groups 2 and 3 (p<0.05). CRP: C-reactive protein; aPTT: activated partial thromboplastin time; PT: Prothrombin time.

Table 5. Regression analysis of risk factors between COVID-19 patients groups

Parameter	B[c]	SE[d]	Walde	p	OR[f] (95% CI)
D-dimer[a]	0.002	0.001	17.377	<0.001	1.002 (1.001–1.003)
D-dimer[b]	0.002	0.001	20.205	<0.001	1.002 (1.001–1.003)
PT[b]	0.986	0.258	14.583	<0.001	2.682 (1.616–4.449)

[a]: Between group 1 and group 2 COVID-19 patients group; [b]: between group 1 and group 3 COVID-19 patients group. B[c]: beta coefficient; SE[d]: Standard errror; Walde: Wald Chi-squared test ; OR[f]: Odds ratio; PT: Prothrombin time; CI: Confidence interval.

In a retrospective study, similar to our study findings, relatively increased D-dimer values in the group with higher (>30 mg/L) CRP values and also a positive correlation between D-dimer and CRP values were reported [20]. Many other researchers have also showed a significant positive correlation between D-dimer and CRP values in COVID-19 patients [21, 22]. In addition, a correlation was found between serum CRP levels and coagulation parameters in our study. D-dimer level was a significant risk parameter between groups.

Fibrinogen and D-dimer, which are used in the monitoring of COVID-19 disease, are two important parameters that predict thromboembolic events associated with hypercoagulopathy [23, 24]. It is known that interleukins produced in the lung induce hyperfibrinogenemia and thrombocytosis with an inflammatory response and cause endothelial damage [25, 26]. Increases in the plasma levels of fibrinogen, and activated platelets accelerate fibrin formation [27, 28].

In our study, a significant shortening of aPTT was observed in the COVID-19 patients, and only between Groups 1 and 2. This shortening may be caused by elevations in fibrinogen, factor VIII and von Willebrand Factor levels in the early phase of the disease [29–31]. Han et al. [17] indicated that PT was shortened in COVID-19 patients, without any difference between stages of COVID-19 disease in terms of aPTT and PT parameters. Zou et al. [18] also found significantly longer PT and aPTT in severe cases rather than in mild cases. Slight prolongation in aPTT that might be seen in COVID-19 disease has been linked to many factors such as heparin usage, the presence of lupus anticoagulant, and increased CRP values [29, 32]. A meta-analysis evaluating coagulation parameters in COVID-19 patients have demonstrated differences in aPTT, and prothrombin times (PT) [22].

In our study, significant prolongation of PT was found in COVID-19 patients compared to the non-COVID-19 patients

and in Group 3 relative to the other groups. In addition, PT was found to be an independent risk factor in Groups 1 and 3.

Similar to our study; in many studies, PT was found to be longer in severely affected patients compared to COVID-19 patients with a good prognosis [6, 8, 20, 33]. PT prolongation is one of the poor prognostic markers. Mild prolongation of aPTT and PT may develop in more severely affected patients who develop disseminated intravascular coagulation [5].

When we evaluate all our findings, we can say that the acute phase reaction is more pronounced at the beginning of the COVID-19 disease and coagulopathy is more prominent in the advanced stage.

The limitations of our study include the fact that it was a retrospective single-center study, and classified COVID-19 positive and negative groups according to PCR test results alone irrespective of the differences in ages of the patients in COVID-19 positive and negative groups. Besides, since our study covered the 1st months of the pandemic in which fibrinogen levels were not measured in all patients, these values were not fully evaluated.

In the early stage of COVID-19 patients, in addition to CRP, elevation of fibrinogen and D-dimer and shortening of aPTT may be important prognostic parameters.

In conclusion; our findings suggest that coagulopathy occurs in the early stage of COVID-19, and is related to the severity of inflammation as stated and defined as COVID-19- associated coagulopathy. It is important to monitor coagulation tests along with markers of inflammation from the early stages of the disease, so as to establish the diagnosis of COVID-19 disease, and predict thrombotic complications.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The University of Health Sciences Tepecik Training and Research Hospital Clinical Research Ethics Committee (No: 2021/06-05, Date: 15/06/2021).

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