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Investigation of ADAMTS-13 levels in patients with COVID-19 infection

Hüseyin H Kutlu[1], Arzu Sahin[2], Soycan Mizrak[3], Abdurrahman Yilmaz[4], Songul Doganay[5], Serdar Gungor[6], Sema Yilmaz[7]

[1] Department of Medical Microbiology, Faculty of Medicine, Usak University, Usak, Turkiye
[2] Department of Physiology, Faculty of Medicine, Usak University, Usak, Turkiye
[3] Department of Medical Biochemistry, Faculty of Medicine, Usak University, Usak, Turkiye
[4] Department of Emergency Medicine, Faculty of Medicine, Usak University, Usak, Turkiye
[5] Department of Physiology, Faculty of Medicine, Sakarya University, Sakarya, Turkiye
[6] Department of Medical Microbiology, Faculty of Medicine, Bilecik University, Bilecik, Turkiye
[7] Department of Pediatric Hematology and Oncology, Faculty of Medicine, Usak University, Usak, Turkiye

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) patients are predisposed to thrombotic events. COVID-19 coagulopathy can be associated with ADAMTS-13 (a disintegrin-like and metalloprotease with thrombospondin type I repeats 13) levels. ADAMTS-13, the cleaving protease of highly thrombogenic ultra-large von Willebrand Factor (vWF) multimers, was rarely investigated in COVID-19 patients and inconsistent results were obtained. We measured ADAMTS-13 levels of patients admitted to emergency department.

Methodology: A prospective study was carried out with 180 individuals at the Emergency Department of Uşak Training and Research Hospital. The patients were divided into three groups: mild COVID-19 (group 2), severe COVID-19 with oxygen saturation below 94% (group 3), and control group (group 1). ADAMTS-13 levels were analyzed with an enzyme linked immunosorbent assay (ELISA) kit (SunRed, Shanghai, China). Demographic data, clinical findings, and routine laboratory test results (alanine aminotransferase (ALT), aspartate aminotransferase (AST), white blood cell, lymphocyte, platelet, C-reactive protein (CRP), lactate dehydrogenase (LDH), prothrombin time, international normalized ratio (INR), partial thromboplastin time, D-dimer, creatinine, urea) were evaluated.

Results: ADAMTS-13 serum levels were slightly lower in groups 2 and 3 compared to the control group, with no significant difference between the ADAMTS-13 median values ($p > 0.05$). Groups 1 and 2 exhibited comparable outcomes. Group 3 demonstrated notably elevated levels of CRP, LDH, D-dimer, AST, ALT, creatinine; and decreased platelet counts and INR levels ($p < 0.05$).

Conclusions: COVID-19-associated coagulopathy is still unclear. Based on our data, ADAMTS-13 levels cannot be used as a biomarker to help stratify patients' risks at the time of admission.

Key words COVID-19; ADAMTS-13; COVID-19-associated coagulopathy.

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Introduction

Coronavirus disease 2019 (COVID-19) is primarily manifested as a respiratory tract infection, but emerging data indicate that it should be regarded as a systemic disease. COVID-19 fatality rates range from 2.3% in general population to 49% among critically ill patients. This mortality burden is attributable to different factors but one of the most important is undoubtedly thromboembolic complications [1]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) enters the host cells via angiotensin converting enzyme receptor 2 expressed in many organs, including in endothelial cells [2]. The viral entry to the endothelial cells or immune-mediated inflammation can lead to diffuse endothelial activation and dysfunction, followed by release of ultra-large von Willebrand factor (vWF) multimers. The multimeric form of vWF is highly thrombogenic due to its capacity of hyper-reactively attaching to platelet glycoprotein Ib-IX-V (GP Ib-IX-V) complex [3].

ADAMTS-13 (a disintegrin-like and metalloprotease with thrombospondin type I repeats 13) is a metalloprotease synthesized by hepatic stellate cells and regulates thrombosis by cleaving ultra-large vWF between the 842nd tyrosine–843rd methionine peptide bonds to generate smaller fragments with low thrombogenicity [3,4]. Deficiency of ADAMTS-13 can not only cause a thrombotic disorder called thrombotic thrombocytopenic purpura, but also activate inflammatory conditions [4]. Consequently, some

studies found a correlation between ADAMTS-13 levels and severity of sepsis, organ dysfunction, or outcome [4,5].

Various studies have shown a higher predisposition to thrombotic events, especially pulmonary embolism, in COVID-19 patients [6]. Some studies have focused on the vWF-ADAMTS-13 relationship to elucidate the unique mechanism in COVID-19 coagulopathy. However, conflicting results have been obtained about ADAMTS-13 levels [7]. Although there are many studies that have found low levels and activity of ADAMTS-13 [8-10], some studies claim otherwise with normal or mildly reduced levels of the enzyme [11-13].

In our study, we aimed to measure ADAMTS-13 levels of patients diagnosed with SARS-CoV-2. In contrast to many studies with a small number of patients who had prolonged hospitalization and received different medications, our study was performed on a higher number of naive patient population without taking any treatment. Oxygen saturations, C-reactive protein (CRP), white blood cells (WBC), lymphocytes (LYM), lactate dehydrogenase (LDH), platelets (PLT), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), activated partial thromboplastin time (APTT), D-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine levels were also recorded.

Methodology

Patients and study design

The prospective study was carried out with a total of 180 individuals (120 patients diagnosed with COVID-19 and 60 patients with non-COVID-19), aged between 18 and 75 years old, who applied to the Emergency Medicine Department between February and August 2021 in Uşak Training and Research Hospital.

Patients who had complaints such as fever, malaise, cough, shortness of breath, muscle pain, loss of taste and smell, headache; and who had a positive real-time polymerase chain reaction (RT-PCR) test were included in the patient group (Group 2 and 3). The patient group was divided into two subgroups: patients with a mild course of COVID-19 (n = 60) who had a positive RT-PCR result, oxygen saturation above 94% [14], and were eligible for home follow-up were included in Group 2; Group 3 (n = 60) included RT-PCR-confirmed COVID-19 patients with an oxygen saturation below 94% and considered to have a severe course of the infection [14]. Patients who applied to emergency department with complaints such as low back pain, knee pain, abdominal swelling, hypertension, trauma and had a negative SARS-CoV-2 PCR test were included in the control group (Group 1). Demographic features of patients were summarized in Table 1.

Exclusion criteria were history of past COVID-19 infection, any treatment modalities for COVID-19, vaccinated status, history of bleeding and coagulation disorders such as hemophilia, thrombotic thrombocytopenic purpura (TTP), factor deficiency, use of anticoagulant drugs, and having chronic heart disease (heart failure, history of previous myocardial infarction) or chronic liver disease.

Age, gender, clinical findings (body temperature, pulse, blood pressure, respiratory rate, oxygen saturation with pulse oximeter), blood chemistry tests (ALT, AST, CRP, LDH, PT, INR, PTT, D-dimer, creatinine, urea), and blood count (WBC, lymphocyte and platelet) were recorded.

Blood sampling and measurement of ADAMTS-13 levels

Peripheral blood was obtained and immediately centrifuged in a refrigerated centrifuge at 4000 rpm for 10 minutes. The serum samples were stored at -80 ºC until ADAMTS-13 analysis was performed. ADAMTS-13 levels were analyzed with an enzyme linked immunosorbent assay (ELISA) kit according to the instructions of the manufacturer (SunRed, Shanghai, China). Spectrophotometric measurements were performed by an ELISA microplate reader (BIOBASE EL-10A, Jinan, China) at a wavelength of 450 nm.

Ethics approval and informed consent

The study protocol was approved by the Clinical Research Ethics Committee of Uşak University Faculty of Medicine (date and number: 12.02.2021-E.7052). Informed consents were obtained in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 24.0 (SPSS Inc., Chicago, USA). Kolmogrov-Smirnov test was used to determine the conformity of the data to normal distribution. Kruskal-Wallis test was used to compare more than two independent samples, and the significance level of the difference between groups was evaluated by Mann Whitney U test. Descriptive analyses were presented using median and interquartile range (IQR) for non-normally distributed variables. Spearman correlation coefficient analysis was applied

Table 1. Comparison of laboratory parameters in study groups*

Parameter	Group 1 (n = 60) Median (IQR)	Group 2 (n = 60) Median (IQR)	Group 3 (n = 60) Median (IQR)	*p* value (Kruskal- Wallis)
Age (years)	39.5 (35)	49 (26)	64.5 (26) [a, b]	0.000
Gender (Female/Male) n - %	31/29; 51.7%-48.3%	27/33; 45%-55%	31/29; 51.7%-48.3%	-
SpO_2	98 (2)	97 (2)	90.5 (6) [a, b]	0.000
WBC	7.60 (2.45)	8.44 (5.47)	8.27 (5.41)	0.382
LYM (IR), K/µL	1.77 (1,25)	2.39 (1.68) [a]	1.34 (1.39) [b]	0.000
PLT	249 (100.75)	245 (93)	215 (136.25) [a]	0.031
AST	18.50 (8.50)	21.50 (11)	27.50 (18) [a, b]	0.000
ALT	20.50 (12.75)	23 (15.75)	26 (26.75) [a, b]	0.018
Urea	14.50 (7.75) [b]	12 (5)	15.50 (28.50) [b]	0.004
Creatinin	0.82 (0.20)	0.83 (0.25)	0.99 (0.50) [a, b]	0.003
CRP	4.10 (14.68)	2.90 (21.10)	73.30 (106.90) [a, b]	0.000
LDH	199.5 (116)	206 (70)	289.5 (136) [a, b]	0.000
D-Dimer (IR), µg FEU/L	461 (560)	365.35 (398)	1105 (1323) [a, b]	0.000
PT (IR), s	11.85 (1.30)	12 (2.50)	11.75 (85.98)	0.841
INR (IR)	1 (0.20)	1 (0.20)	0.90 (0.10) [a, b]	0.003
APTT	24.70 (4.17)	25.70 (5.05)	25.85 (6.17)	0.220
ADAMTS-13 (ng/mL)	2.12 (1.5)	2.08 (1.19)	2.04 (1.11)	0.222

*Results are given as median and interquartile range (IQR). [a] Statistically different from Group 1, [b] Statistically different from Group 2. ADAMTS-13: a disintegrin-like and metalloprotease with thrombospondin type I repeats-13; ALT: alanine transaminase; APTT: activated partial thromboplastin clotting time; AST: aspartate aminotransferase; CRP: C-reactive protein; INR: international normalized ratio; LDH: lactate dehydrogenase; LYM: lymphocyte; n: number; PLT: platelet; PT: prothrombin time; SpO_2: oxygen saturation; WBC: white blood cell.

to investigate the correlation relationship. Pearson's χ^2 test was used to compare categorical variables between the two groups. Categorical variables were presented as frequency (%). A p value of < 0.05 was considered statistically significant.

Results

A total of 120 COVID-19 patients diagnosed with SARS-CoV-2 RT-PCR test and 60 non-COVID patients, with almost the same female/male ratio (49.4/50.6) and aged between 18-75 years were evaluated.

The median ages of the 60 non-COVID-19 controls (Group 1); 60 patients with mild respiratory symptoms (coughing, loss of taste and smell, low grade fever without dyspnea), and an oxygen saturation above 94 (Group 2); and 60 patients with severe respiratory symptoms (high grade fever, coughing with dyspnea, severe malaise) and an oxygen saturation below 94 (Group 3) were 39.5 years, 49 years, and 64.5 years respectively. The difference between the median ages was statistically significant between Group 1 and Group 3 ($p = 0.000$) and between Group 2 and Group 3 ($p = 0.000$).

In terms of gender distribution, Group 1 consisted of 31 females (51.7%) and 29 males (48.3%), Group 2 consisted of 27 females (45%) and 33 males (55%), and Group 3 consisted of 31 females (51.7%) and 29 males (48.3%).

Although ADAMTS-13 serum levels were slightly lower in the patient groups [Group 2: 2.08 ng/mL, median; 1.19 ng/mL, interquartile range; and Group 3: 2.04 ng/mL, median, 1.11 ng/mL, interquartile range; compared to the control group (2.12 ng/mL, median; 1.5 ng/mL, interquartile range)], there was no significant difference between the ADAMTS-13 median values between the groups ($p > 0.05$). Comparison of the other laboratory parameters of the patients according to the groups and their statistical significance are presented in Table 1.

Correlation analysis was performed to test the relationship between ADAMTS-13 levels and laboratory parameters. No statistically significant correlation was found between ADAMTS-13 levels and other laboratory parameters (Table 2).

There was a negative correlation between CRP and lymphocyte count ($r = -0.336$, $p = 0.000$), CRP and platelet count ($r = -0.212$, $p = 0.004$), and CRP and INR ($r = -0.203$, $p = 0.006$). There were positive correlations between CRP and LDH ($r = 0.470$, $p = 0.000$), CRP and D-dimer ($r = 0.573$, $p = 0.000$), CRP and AST ($r = 0.310$, $p = 0.001$), CRP and urea ($r = 0.231$, $p = 0.011$), and CRP and creatinine ($r = 0.386$, $p = 0.000$) (Table 2). There was a significant negative correlation between D-dimer and SpO_2 ($r = -0.418$, $p = 0.000$), and D-dimer and platelet count ($r = -0.185$, $p = 0.013$); while there were significant positive correlations between D-dimer and urea ($r = 0.299$, $p = 0.001$), D-dimer and creatinine ($r = 0.389$, $p = 0.000$), and D-dimer and AST ($r = 0.212$, $p = 0.020$). Other correlations are listed in Table 2.

Discussion

COVID-19 can manifest with thrombotic events like pulmonary embolism or venous thromboembolism

Table 2. Correlation between ADAMTS-13 and biochemical parameters.

	A-13	**CRP**	**LYM**	**WBC**	**PT**	**LDH**	**D-dimer**	**SpO_2**	**PLT**	**INR**	**APTT**	**AST**	**ALT**	**Urea**	**Cre**
A-13	1.000	0.032	-0.112	0.010	0.115	-0.045	-0.057	0.052	0.034	0.048	-0.038	-0.065	0.022	-0.115	0.025
p	-	0.670	0.134	0.890	0.126	0.549	0.450	0.490	0.649	0.522	0.612	0.383	0.769	0.125	0.741
CRP		1.000	-0.336	0.158	0.070	0.470	0.573	-0.493	-0.212	-0.203	0.028	0.310	0.067	0.231	0.386
p		-	**0.000****	0.034	0.350	**0.000****	**0.000****	**0.000****	**0.004***	**0.006***	0.711	**0.001***	0.468	**0.011***	**0.000****
LYM			1.000	0.292	-0.216	-0.301	-0.279	0.198	0.276	-0.060	-0.086	-0.013	0.200	-0.206	-0.131
p			-	**0.000****	0.004*	**0.000****	**0.031***	**0.008***	**0.000****	0.422	0.711	0.885	**0.028***	**0.024***	0.154
WBC				1.000	-0.144	0.022	0.107	-0.044	0.377	0.028	0.017	-0.020	0.073	0.191	0.158
p				-	0.054	0.768	0,155	0.555	**0.000****	0.705	0.823	0.829	0.429	**0.037***	0.085
PT					1.000	0.036	0.029	-0.030	-0.042	0.290	0.334	-0.027	-0.017	0.201	0.247
p					-	0.630	0.700	0.687	0.579	**0.000****	**0.000****	0.773	0.853	**0.028***	**0.007***
LDH						1.000	0.304	-0.286	-0.183	-0.097	0.059	0.482	0.206	0.304	0.294
p						-	**0.000****	**0.000****	**0.014***	0.195	0.430	**0.000****	**0.024***	**0.001***	**0.001***
D-dimer							1.000	-0.418	-0.185	-0.047	-0.085	0.212	0.034	0.299	0.389
p							-	**0.000****	**0.013***	0.533	0.259	**0.020***	0.711	**0.001***	**0.000****
SpO_2								1.000	0.163	0.208	0.017	-0.299	-0.107	-0.283	-0.323
p								-	**0.029***	**0.005***	0.821	**0.001***	0.246	**0.002***	**0.000****
PLT									1.000	0.006	-0.081	0.009	0.061	-0.023	-0.063
p									-	0.934	0.277	0.923	0.510	0.799	0.496
INR										1.000	0.167	-0.038	0.054	0.145	0.095
p										-	**0.025***	0.678	0.557	0.114	0.300
APTT											1.000	-0.012	-0.036	0.150	0.221
p											-	0.897	0.698	0.103	**0.015***
AST												1.000	0.596	0.126	0.247
p												-	**0.000****	0.171	**0.007***
ALT													1.000	0.007	0.114
p													-	0.944	0.214
Urea														1.000	0.514
p														-	**0.000****
Cre															1.000
p															-

Results were expressed as correlation coefficient and *p* values. *$p < 0.05$, **$p < 0.001$ were considered significant. A-13 or ADAMTS-13 (ng/mL), a disintegrin-like and metalloprotease with thrombospondin type I repeats-13; ALT: alanine transaminase; APTT: activated partial thromboplastin clotting time; AST: aspartate aminotransferase; Cre: creatinin; CRP: C-reactive protein; INR: international normalized ratio; LDH: lactate dehydrogenase; LYM: lymphocyte; n: number; PLT: platelet; PT: prothrombin time; SpO_2: oxygen saturation; WBC: white blood cell.

(VTE) [6]. vWF and its cleaving protease, ADAMTS-13, play a central role in microvascular hemostasis, and an imbalance in vWF-ADAMTS-13 axis can contribute to thromboembolic events [6].

There were inconsistent results in studies investigating ADAMTS-13 levels in COVID-19 patients. Some studies indicated a reduction in ADAMTS-13 levels or activities which can correlate with increased coagulopathy and mortality of COVID-19 patients [8–10,15]. Bazzan *et al.* investigated plasma levels of ADAMTS-13 and vWF in 88 RT-PCR-confirmed COVID-19 patients and found significant reduction in ADAMTS-13 levels of all patients compared to healthy controls [8]. Another study from Italy revealed reduced ADAMTS-13 activity in 50 COVID-19 patients stratified according to disease severity but none presented a severe deficiency of the activity levels [9]. In a case series of three patients, all patients showed low ADAMTS-13 levels, but also positive antiphospholipid antibodies [10]. Morici *et al.* found lower plasma ADAMTS-13 in 5 of 6 tested patients [15]. Tiscia *et al.* argued that patients with ADAMTS-13 activity below median value had a significantly lower survival [16]. On the contrary, our study revealed no significant decrease in ADAMTS-13 levels between the control group including non-COVID-19 patients (Group 1), patients with mild respiratory symptoms (Group 2), and patients with severe respiratory symptoms of COVID-19 (Group 3).

Our study findings were not alone in this context. In contrast to the studies that found low ADAMTS-13 levels, there are also studies to claim otherwise with normal or mildly reduced levels of the enzyme. In a prospective controlled trial performed on 75 patients of mild to critical severity, ADAMTS-13 activities were not significantly different from healthy controls [11]. Escher *et al.* found normal ADAMTS-13 activity in their 3 COVID-19 patients suggesting that low enzyme levels may not play an important role in COVID-19 coagulopathy [13]. In our study, ADAMTS-13 serum levels were slightly lower in the patient groups compared to the control group, but there was no significant difference between the ADAMTS-13 median values. ADAMTS-13 levels have been a rarely investigated issue in studies on COVID-19 [11]. In the few studies that analyzed ADAMTS-13 levels or activities, samples were collected a long time after the patients' admission to the hospital, usually during intensive care stay. In the study of Mancini *et al.* patient blood samples were collected at a median time of 13 days after admission to the emergency department [9]. In another study from Italy, ADAMTS-13 levels were measured on blood samples obtained within seven days after hospitalization [16]. In our study, ADAMTS-13

levels were evaluated from blood samples taken at the time of hospital admission. Our study results revealed that ADAMTS-13 cannot be used as a biomarker to help stratify patients' risks at the time of admission.

Another arguable issue is whether ADAMTS-13 reduction in some studies is due to consumption of the enzyme, or due to side effects of the treatments, or damage of organs such as the liver. Hepatic stellate cells (HSC) play a pivotal role in ADAMTS-13 production. Plasma ADAMTS-13 activity decreased in experimental HSC apoptosis model or in 70% hepatectomized rats [17]. Plasma ADAMTS-13 levels significantly reduced in liver cirrhosis proportional to the severity of the cirrhosis [18]. COVID-19-associated liver damage can occur due to direct infection by SARS-CoV-2, or iatrogenic factors such as drugs and ventilation may lead to damage [19]. Due to limited evidence-based information at the beginning of the COVID-19 pandemic, various treatment modalities were tried. Most of these drugs such as remdesivir and ritonavir are known to have hepatotoxic effects [19]. Corticosteroid therapy, which is recommended in severe COVID-19 infection, is also associated with steatosis [19]. Unlike other studies, the patients included in our study were not taking any medication at the time we took blood samples for ADAMTS-13 measurement. In the blood samples taken, liver function tests were normal in Group 1 (control) and Group 2 (mildly symptomatic COVID-19), while there were moderate increases in ALT and AST values in patients in Group 3 (severe COVID-19 symptoms).

Consistent with other studies, our patients with low oxygen saturation (Group 3) had significantly higher CRP, LDH, D-dimer, AST, ALT, creatinine levels and lower platelet and INR levels. Laboratory tests were used to assess prognosis and progression of the disease. Significant changes in laboratory findings, such as increased CRP, D-dimer levels, elevated LDH, AST, urea, creatine kinase (CK), high-sensitivity troponin I, and decreased lymphocyte counts are common laboratory markers of severe COVID-19 infection [20]. But there was no statistically significant correlation between ADAMTS-13 levels and other laboratory parameters.

Limitations of the study

The contribution of taking any medication at the time of blood sampling on ADAMTS-13 levels is not known and new studies to understand this aspect may be necessary.

Conclusions

COVID-19-associated coagulopathy is still unclear to scientists. According to our findings, ADAMTS-13 levels cannot be used as a biomarker to help stratify patients' risks at the time of admission. In our study, ADAMTS-13 levels did not show a significant decrease in COVID-19 patients and for this reason we conclude that the contribution of ADAMTS-13 levels to the microangiopathic state is limited. However, further research is necessary to elucidate inconsistent results on ADAMTS-13 levels or activity and the unique mechanism of COVID-19 associated coagulopathy.

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Notes

The work was conducted in Usak University Faculty of Medicine, Turkey. Sema Yilmaz is currently retired.

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Corresponding author

Hüseyin Haydar Kutlu, MD.
Department of Medical Microbiology, Faculty of Medicine,
Usak University, 1 Eylül Campus, Uşak/Turkiye.
Tel: +90 506 6875647
Email: hhaydarkutlu@gmail.com, huseyin.kutlu@usak.edu.tr

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