EVALUATION OF ADAMTS 13 AS A BIOMARKER OF STRONG INFLAMMATION AND ENDOTHELIAL DAMAGE IN COVID 19 PATIENTS

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Abstract

Background: A considerably marked increase in inflammation markers has been observed in patients with COVID-19 disease, this proinflammatory state can cause endothelial dysfunction, ultrastructural features of endothelial cell distribution and SARS-COV2 visible within the cell have been described in patients who died from COVID-19.

Aim: to assess the possible involvement of ADAMTS13 in the coagulopathy associated with COVID-19.

Methods: This retrospective study conducted on 66 cases were divided into 3 groups; Group (I): (22) moderately diseased patient at isolation room. Group (II): (22) severe diseased patient in intensive care. Group (III): (22) apparently healthy individuals of mating age and sex with negative PCR for COVID.

Results: there was a statistically significant increase in CRP, bilirubin among severe cases compared to non-severe. There was a statistical significance difference between the studied groups in ADAMTS 13. Post hoc test showed that there was a statistical significance decrease in ADAMTS 13 among severe cases compared to non-severe and control and among non-severe cases compared to control. ADAMTS 13 at cut off <1199.4 ng/ml had sensitivity 90%, specificity 90% and accuracy 90% in diagnosis of COVID-19. Moreover, ADAMTS 13 at cut off <575.49ng/ml had sensitivity 75%, specificity 65% and accuracy 70% in diagnosis of severe COVID-19 among cases groups.

Conclusion: Decreased ADAMTS13 associated with unfavorable outcomes of patients with COVID-19.

Keywords: ADAMTS 13; COVID 19; Endothelial Damage; inflammatory markers

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Introduction

An outbreak of a viral respiratory illness (named COVID-19 officially by WHO) started in December 2019, in the city of Wuhan. Hubei province, China. On March 11,2020 the WHO declared COVID-19 to be pandemic (**1)**. Disease symptoms range from absence of symptoms, mild symptoms, including fever, dry cough, muscle pain, and gastrointestinal symptoms such as nausea, diarrhea, vomiting, and severe symptoms**.** In severe cases, the disease may deteriorate, leading to pneumonia, acute respiratory distress syndrome (ARDS), multi-organ complications, and death **(2).**

A considerably marked increase in inflammation markers has been observed in patients with COVID-19 disease **(3).** Furthermore ultrastructural features of endothelial cell destruction and SARS-COV2 visible within the cell have been described in patients who died from COVID-19 **(4).**

Multiple studies had reported higher rates of thrombosis and coagulopathy among COVID-19 patients; it was called later Coronavirus-associated coagulopathy (CAC). International Society of Thrombosis and Hemostasis (ISTH) has recently released the frequently observed clinical characteristics of CAC among COVID-19 patients. They included elevated D-dimer, slightly decreased platelet count, and abnormal prothrombin time (PT) **(5).**

The role of the interaction between VWF and ADAMTS13 among COVID-19 is not widely studied. Although studies report abnormal levels of ADAMTS13 among COVID-19 patients, these studies were mainly case-reports with a small sample size. Also, they had not drawn enough explanation of the pathophysiology of CAC **(6,7).**

Thus, this study aimed to assess the possible involvement of ADAMTS13 in the coagulopathy associated with COVID-19 and its relevance in the severity and prognosis of the infection.

Subjects and Methods

This Observational, descriptive case control study was carried out at COVID-19 isolation unit of internal medicine department, Faculty of Medicine, Zagazig University, and Clinical Pathology Department, Faculty of Medicine, Zagagzig University. This study is carried out on 44 consecutive PCR-Proven COVID-19 hospitalized patients and 22 apparently healthy control.

Patients are classified into 3 groups according to the severity of COVID-19 disease.

Group (I): included 22 moderately diseased patients at isolation room.

Group (II): included 22 severe diseased patients in intensive care.

Group (III): included 22 healthy individuals of matching age and sex with negative PCR for COVID.

Inclusion Criteria:

Patients were positive for SARS-CoV-2 as confirmed by reverse-transcriptase–polymerase-chain-reaction real-time (RT-PCR) assay by nasopharyngeal swabs under aseptic operation. Patients in the study were hospitalized adult COVID-19 patients aged 30- 80 with different disease severity grades, who had serum ADAMTS13 activity test done.

Exclusion Criteria:

Patients who had not the test were excluded

Clinical assessment:

Full history taking and complete clinical examination: according to the included work sheet with special attention to age, sex, and an individual had close contact with someone diagnosed with COVID-19 or travelled to or lived in any areas with ongoing community spread of COVID-19 within last 14 days.

Full clinical examination was performed. Symptoms may vary from mild cough to fulminant respiratory failure. Positive tests have also been obtained from asymptomatic patients. Symptoms may be cough, Fever, Fatigue, Dyspnea, GI symptoms (Diarrhea, nausea and vomiting).

Patients were classified as severe; if at least one of the following criteria was met; hypoxemia in need for invasive mechanical ventilation, D-dimer plasma concentration >3000 ng/mL and at least three of the next: CRP > 15 mg/dL, ferritin >1000 ng/mL, D-dimer > 1,500 ng/mL, lymphopenia < 800 x 109/L and/or IL-6 > 40. 22 patients were classified as severe COVID-19 disease cases and 22 moderate as form of COVID-19 disease. Blood samples were collected at patient's admission.

Routine laboratory investigations including Complete blood count (CBC): by automated cell counter “Sysmex XS” XN2000 (Sysmex Corporation, Japan), Coagulation Profile.: PT, PTT & INR**,** Qualitative C- Reactive Protein (CRP): by latex agglutination test, and D-Dimer by Roche/Hitachi analyzers and Cobas C analyzers**.**

Measurement of serum ADAMTS-13 level by ELISA:
ADAMTS-13 was measured using the Human Von Willebrand Factor Cleaving Protease (vWFCP) double antibody sandwish ELISA technique kit.

Radiological diagnosis
1- X-ray: Plain chest X-rays are less sensitive than computed tomography, but may evidence sparse bilateral consolidations accompanied by ground glass opacities, peripheral/subpleural images, predominantly in the lower lobes**.**
2- CT: Computed tomography of the chest presents greater sensitivity and reveals multifocal, bilateral, peripheral/subpleural ground glass opacities, generally affecting the posterior portions of the lower lobes, with or without consolidations**.**

Statistical Analysis
Data was analyzed using SPSS 21 (Statistical Package for the Social Services) (SPSS). The findings were displayed using both tabular and graphical formats. Results were displayed using standard statistical measures such as means, medians, standard deviations, and confidence intervals. The accuracy of the data was demonstrated with the help of statistics. The student's t test (T) is utilized. Pearson Chi-Square and Chi-Square for Linear Trend were used to analyze the quantitatively diverse data (X2). In this example, a P value of 0.05 or less was judged statistically significant.

Results
The current study showed no statistical significance differences between the studied groups in age or sex distribution **(Table 1).** There were no statistical significance differences between the studied groups in CBC results. But there was a statistical significant increase in CRP among severe cases compared to non-severe **(Table 2)**. There were no statistical significance differences between the studied groups in creatinine, ALT or AST level. But there was a statistical significant increase in bilirubin among severe cases compared to non-severe **(Table 3)**.
There was a statistical significance difference between the studied groups in ADAMTS-13. Post hoc test showed that there was a statistical significance decrease in ADAMTS-13 among severe cases compared to non-severe and control and also among Non-severe cases compared to control **(Table 4)**.
There was a statistical high significance -ve correlation between ADAMTS 13 and D.Dimer among the studied cases groups **(Table 5)**. ADAMTS 13 at cut off <1199.4 ng/ml had sensitivity 90%, specificity 90% and accuracy 90% in diagnosis of COVID-19 **(Table 6, Figure 1)**. ADAMTS 13 at cut off <575.49 ng/ml had sensitivity 75%, specificity 65% and accuracy 70% in diagnosis of severe COVID-19 among cases groups **(Table 7, Figure 2)**.

Table (1): Demographic data of the studied groups:

Variable		**Non severe cases (n=20)**		**Severe cases (n=20)**		**Control (n=10)**		**F**	**P**
Age: (years)	Mean ± SD Range	66.6±11.2 36-85		66.5±12.41 30-90		60.4±13.24 35-70		1.03	0.36 NS
Variable		**No**	**%**	**No**	**%**	**No**	**%**	χ^2	**P**
Sex:	Female Male	10 10	50 50	10 10	50 50	5 5	50 50	0	1 NS

SD: Stander deviation, F: ANOVA test χ^2: Chai square test.
NS: Non significant (P>0.05)

Table (2): CBC & CRP results among the studied cases groups:

Variable		**Non severe cases (n=20)**	**Severe cases (n=20)**	**t/MW**	**P**
Hb: (gm/dl)	Mean ± SD Range	10.98±2.34 7.5-16.6	10.88±2.21 6.7-15	0.14	0.89 NS
WBCs: (x10^3/mm^3)	Mean ± SD Range	10.45±5.42 9.35 1.2-20.7	10.6±5.42 9.65 2.4-24.2	0.05	0.96 NS
Platelets:(x10^3/mm^3)	Mean ± SD Range	224.05±146.76 176.5 41-504	284.65±160.99 207 51-610	1.33	0.19 NS
CRP: (mg/dl)	Mean ± SD Range	54.18±50.30 34.82 3.51-169.95	88.55±91.18 44.13 3.2-317.58	1.98	0.049*

SD: Stander deviation, t: Independent t test MW: Mann Whitney test,
*NS: Non significant (P>0.05) *: Significant (P<0.05)*

Table (3): LFTs & KFTs results among the studied cases groups:

Variable		Non severe cases (n=20)	Severe cases (n=20)	MW	P
Creatinine: (mg/dl)	Mean ± SD Median Range	1.13±0.45 1.06 0.38-2.1	1.18±1.05 0.86 0.23-4.09	1.08	0.28 NS
ALT: (IU/L)	Mean ± SD Median Range	20.57±12.33 15.85 11.2-62.1	24.36±11.02 23.75 8.7-46.9	1.38	0.17 NS
AST: (IU/L)	Mean ± SD Median Range	27.99±12.03 25.75 14.2-60	26.56±10.53 23 14.9-46.3	0.46	0.65 NS
Bilirubin: (mg/dl)	Mean ± SD Median Range	0.54±0.23 0.54 0.11-1.2	0.90±0.62 0.78 0.27-2.8	**2.18**	**0.03***

*SD: Stander deviation, t: Independent t test MW: Mann Whitney test, NS: Non significant (P>0.05) *: Significant (P<0.05)*

Table (4): Adminsitegrin and metalloprotease with thrombospodin motif 13 (ADAMTS-13) among the studied groups:

Variable		Non severe cases (n=20)	Severe cases (n=20)	Control (n=10)	KW	P	Post hok
ADAMTS 13: (ng/ml)	Mean ± SD Median Range	873.96±597.56 708.18 327.33-2396.26	513.78±101.74 505.63 319.32-740.02	1553.57±435.42 1372.3 1172.12-2396.26	**21.54**	**<0.001*** *	**0.02*[1]** **0.002*[2]** **<0.001**[3]**

*SD: Stander deviation, KW: Kruskal Wallis test, *: Significant (P<0.05) **: Highly significant (p<0.001) Post hoc: P1: Non severe versus severe cases, P2: Non severe cases versus control, P3: Severe cases versus control*

Table (5): Correlation between ADAMTS-13 and studied variables (age & Laboratory parameters) among the studied cases groups:

Variable	ADAMTS-13 (n=40)	
	r	P
Age (years)	0.13	0.53 NS
Hb (gm/dl)	0.25	0.12 NS
WBCs (x10^3/mm^3)	0.18	0.25 NS
Platelets (x10^3/mm^3)	-0.25	0.11 NS
CRP (mg/dl)	-0.03	0.89 NS
Creatinine (mg/dl)	-0.07	0.65 NS
ALT (IU/L)	0.22	0.18 NS
AST (IU/L)	0.14	0.38 NS
Bilirubin (mg/dl)	0.09	0.57 NS
INR	0.17	0.30 NS
D.Dimer (mg/L FEU)	**-0.76**	**<0.001****

r*: Spearman's correlation coefficient. NS: Non significant (P>0.05) *: Significant (P<0.05)**: Highly significant (P<0.001)*

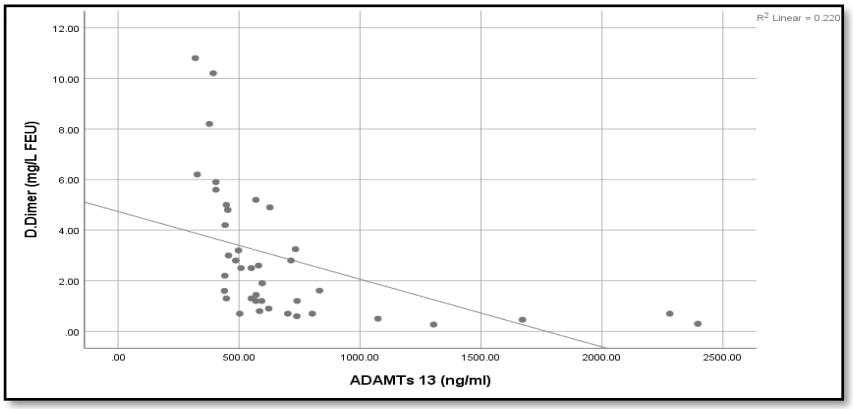

Figure (1): Negative Correlation between ADAMTS-13 & D.Dimer among the studied cases groups.

Table (6): Validity of ADAMTS-13 in diagnosis of COVID-19 among the studied groups:

Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
<1199.64 ng/ml	0.93 0.85-1	90%	90%	97.3%	69.2%	90%	**<0.001****

AUC: Area under curve CI: Confident interval PPV: +ve predicted value NPV:-ve predicted value
***: Highly significant (P<0.001)*

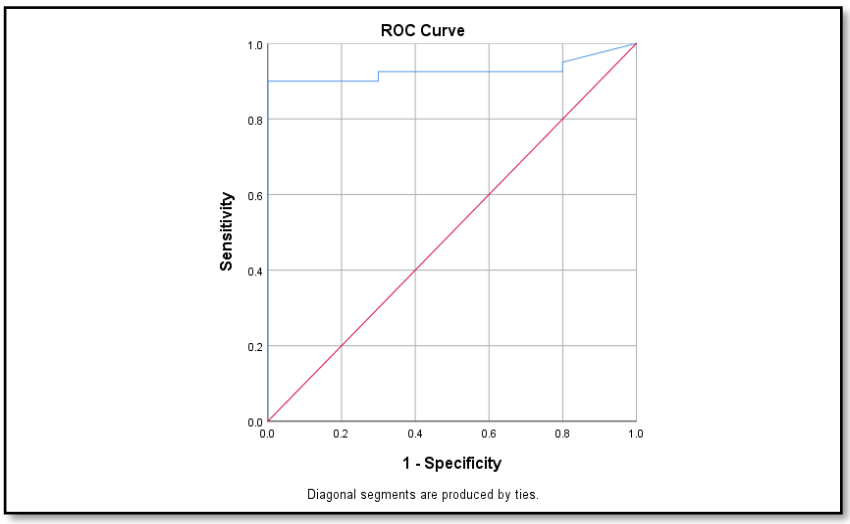

Figure (2): Roc curve for ADAMTDS-13 Validity in COVID-19 diagnosis among the studied groups.

Table (7): Validity of ADAMTS-13 in diagnosis of severe COVID-19 among the studied cases groups:

Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
<575.49 ng/ml	0.70 0.53-0.87	75%	65%	68.2%	72.2%	70%	**0.03***

*AUC: Area under curve CI: Confidante interval PPV: +ve predicted value NPV:-ve predicted value *: significant (P<0.05)*

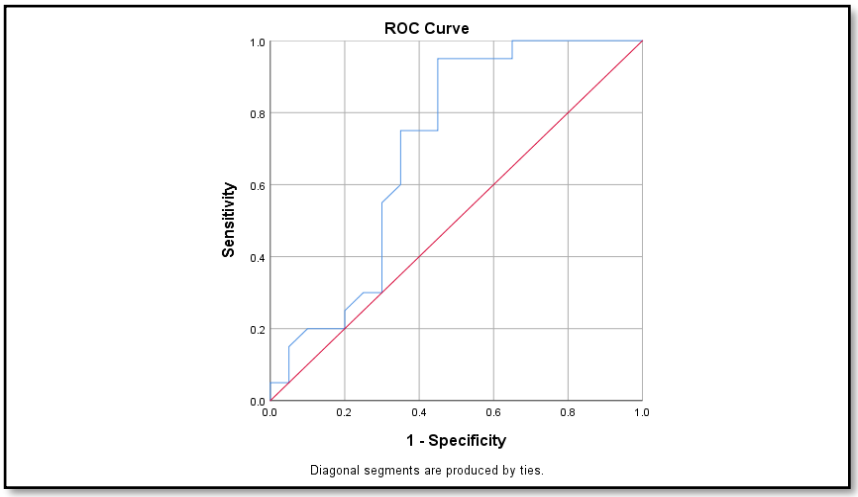

Figure (3): Roc curve for Validity of ADAMTS-13 in diagnosis of severe COVID-19 among the studied cases groups.

Discussion

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) have been reported to develop endothelium injury, an excessive inflammatory response and subsequent marked hypercoagulability leading to prevalence of venous thromboembolic events **(8).**

Disease symptoms range from absence of symptoms, mild symptoms, including fever, dry cough, muscle pain, and gastrointestinal symptoms such as nausea, diarrhea, vomiting, and

severe symptoms **(9).** In severe cases, the disease may deteriorate, leading to pneumonia, acute respiratory distress syndrome (ARDS), multi-organ complications, and death **(10).**

In severe COVID-19, microthrombi may form onto the membrane of endothelial cells, where a significant amount of local inflammation leads to endothelial activation and massive release of VWF, altering the local relative concentration of VWF, platelets, and ADAMTS13 **(11)**.

Patients with ADAMTS13 activity below 70 U/dL have a higher risk of in-hospital death **(12).** Their findings are consistent with those observed in patients with sepsis, in whom low ADAMTS13 levels are inversely correlated with vWF15 and a poor prognosis, as well as with sepsis severity **(13)**.
D-dimer, a blood parameter routinely investigated in SARSCoV-2 patients for the possible clinical impact on mortality in these settings, strongly predicts ADAMTS13 levels (G. L. Tiscia et al., 2020). Thus, it is conceivable that endothelial dysfunction could be reflected in any of the hemostasis phases and variables, including the natural anticoagulants. Endothelial dysfunction is a key finding and major determinant of poor prognosis in SARS-CoV-2 patients **(14)**.

The current study showed that there were no statistical significance differences between the studied groups in age or sex distribution. Our findings are in agreement with **Joly et al. (8)** who showed in their study on 53 patients to investigate clinical features, hemostatic laboratory parameters, VWF/ADAMTS13 axis, and ADAMTS13 conformation in critically ill COVID-19 patients at admission that there were no statistical significance differences between the studied groups in age or sex distribution.
The present findings regarding CBC and CRP parameters showed that there was a statistical significant increase in CRP among severe cases compared to non-severe.

The present study was in line with **Joly et al. (8) & Fernandez et al. (15)** reported that there was a statistical significant increase in CRP among severe cases compared to non-severe.
Regarding LFTs and KFTs parameters in the present study, there was a statistical significant increase in bilirubin among severe cases compared to non-severe.

The present study was agreed with **Tiscia et al. (12)** reported that there was significant difference between groups regarding ALT and bilirubin. Also **Sweeney et al. (16)** reported that Initial markers of renal function were significantly worse in nonsurvivors compared with survivors whereas markers of liver function were not significantly different.

Regarding blood coagulation profile in the current study, there was a statistical significant increase in D-dimer among severe cases compared to non-severe. Our findings were in the same line with **Tiscia et al. (12)** reported that there was significant difference between groups regarding PTT and D-dimer. Moreover, **Sweeney et al. (16)** reported that Initial D-dimer was significantly higher in nonsurvivors.

SARS-CoV-2 infection leads to severe inflammatory response and hypercoagulability with markedly increased fibrinogen, factor V, D-dimers, and IL-6 levels in critically ill COVID-19 patients at ICU admission, with both latter biologic parameters correlating with mortality **(17)**. The present study was agreed with **Fernandez et al. (15)** reported that the mean D-dimer level at admission was 600 ng/ml. The mean D-dimer levels were 500, 800, and 1050 ng/ml in moderate, severe, and critical groups respectively.
The current results revealed that the mean ADAMTS-13 level was 873.96 and 513.78 ng/ml in non-severe and severe groups, respectively. There was a statistical significance difference between the studied groups in ADAMTS 13. Post hoc test showed that there was a statistical significance decrease in ADAMTS 13 among severe cases compared to non-severe and control and among non-severe cases compared to control. Our results were in line with **Joly et al. (8)** reported that median ADAMTS13 activity was significantly lower in non-survivor patients when compared with survivor patients. Also, ADAMTS13 antigen levels were not significantly different between survivors.

Consumption of the metalloprotease ADAMTS13 by its massively increased substrate, VWF, in line with strong inflammation and endothelial damage and/or a partial catalytic inhibition of ADAMTS13 by IL-6 and other cytokines released during the cytokine storm in severe COVID-19 **(18)**.

The present study was confirmed by **Tiscia et al. (12)** reported that nonsurvivors had significantly lower ADAMTS13 activity levels**.**

Our results were disagreed with **Philippe et al. (19)** reported that all non-critical patients showed ADAMTS-13 levels in the normal range.

In **Hafez et al. (20)** study, there was a decrease in ADAMTS13 activity with increasing severity of COVID-19, which could be attributed to the massive production of cytokines, endothelial activation with subsequent exocytosis of WBPs, and VWF**.**

According to the linear regression model, **Hafez et al. (20)** could not find an association between D-dimer concentration and ADAMTS13 activity; this was in opposition to the present results. This difference could be attributed to different patient characteristics in both studies.

The present results showed that ADAMTSS-13 at cut off <1199.4 ng/ml had sensitivity 90%, specificity 90% and accuracy 90% in diagnosis of COVID-19. Moreover, ADAMTS 13 at cut off <575.49 ng/ml had sensitivity 75%, specificity 65% and accuracy 70% in diagnosis of severe COVID-19 among cases groups. However, when considering our data combined with those of the recent literature, it seems more reasonable to think that ADAMTS13 is biomarker reflecting the severity of the endothelial disease caused by SARS-CoV-2 infection (and collateral prognosis biomarkers) rather than strong pathophysiologic actors of the microthrombotic process of COVID-19-associated acute respiratory distress syndrome (ARDS) **(21)**.

This interpretation is further supported by our main result showing that SARS-CoV-2 is not an infectious agent able to induce an open conformation of ADAMTS13, a biological feature that could be one of the triggers for the preliminary step to immune-mediated ADAMTS13 deficiency **(22)**.

Conclusion

Predicting the course of a COVID-19 patient's disease after hospitalization is essential to improve treatment. ADAMTS-13 may assist clinicians in the assessment of care intensity in this setting. Decreased ADAMTS13 associated with unfavorable outcomes of patients with COVID-19. Our findings add knowledge to understanding COVID-19, contributing to widening the data collection on prognostic biomarkers that are potentially helpful in identifying patients with a worse prognosis.

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Author contribution: Authors contributed equally in the study.

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