Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Reduced ADAMTS13 Activity in Correlation with Pathophysiology, Severity, and Outcome of COVID-19: A Retrospective Observational Study

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ABSTRACT

Background: Low ADAMTS13 activity has been suggested to be an interplaying factor in the pathogenesis of COVID-19, considering that it is a thromboinflammatory disease with high risk of microthrombosis.
Objectives: The study aimed to explore the correlation between ADAMTS13 activity and the pathophysiological pathway of COVID-19.
Methods: We carried out a retrospective observational study of 87 patients with COVID-19 in NMC Royal Hospital, Abu Dhabi, UAE. ADAMTS13 activity was measured and compared with patients' characteristics and clinical outcomes.
Results: Low ADAMTS13 activity was associated with pneumonia ($p = 0.007$), severity of COVID-19 ($p < 0.001$), and mechanical ventilation rates ($p = 0.018$). Death was more frequently observed among patients (5 patients) with low ADAMTS13 activity compared with normal activity (1 patient), as well as inflammatory markers. Decreased ADAMTS13 activity increased with the risk of pneumonia, severity of COVID-19, need for mechanical ventilation, and use of anticoagulants ([OR = 4.75, 95% CI 1.54–18.02, $p = 0.011$], [OR = 6.50, 95% CI 2.57–17.74; $p < 0.001$], [OR = 4.10, 95% CI 1.29–15.82; $p = 0.024$], [OR = 8.00, 95% CI 3.13–22.16; $p < 0.001$], respectively). The low ADAMTS13 activity group had a slightly longer time to viral clearance than the normal ADAMTS13 activity group, but it was not statistically significant (20 days, 95% CI 16–27 days vs 17 days, 95% CI 13–22 days; $p = 0.08$; Log rank = 3.1).
Conclusions: Low ADAMTS13 activity has been linked to pneumonia, COVID-19 severity, use of anticoagulants, and need for mechanical ventilation but not to mortality. We propose rADAMTS13 as a novel treatment for severe COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is an endemic disease that first appeared in China in December 2019. The causative organism was identified later; it is an RNA virus that belongs to the Coronaviridae family and is named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lu et al., 2020).

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

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CAC, Coronavirus-associated coagulopathy; rADAMTS13, Recombinant ADAMTS13; TMA, Thrombotic microangiopathy; VWF, von Willebrand factor; UAE, United Arab Emirates; WPBs, Weibel-Palade bodies.

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symptoms (Rothe et al., 2020). In severe cases, the disease may deteriorate, leading to pneumonia, acute respiratory distress syndrome (ARDS), multiorgan complications, and death (Uddin et al., 2020).

Multiple studies had reported higher rates of thrombosis and coagulopathy among patients with COVID-19; 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 patients with COVID-19. They included elevated D-dimer, slightly decreased platelet count, and abnormal prothrombin time (PT) (Franchini et al., 2020).

A case study of a patient with COVID-19 who developed acute portal vein thrombosis (PVT) reported abnormal coagulation tests including D-dimer, Von-Willebrand Factor (VWF), and fibrinogen, and thrombosis symptoms were relieved within 48 hours after treatment with anticoagulants (La Mura et al., 2020). In addition, the prevalence of thrombotic complications among patients with COVID-19 admitted to the ICU ranged from 16%-69% according to several studies (Wool & Miller, 2021).

A study of 23 autopsies of COVID-19 deaths reported an association among CAC, vascular damage, and Endotheliitis (Buja et al., 2020). Another autopsy study also reported microthrombi inside small lung arteries and glomerular capillaries among COVID-19 decedents (Carsana et al., 2020). These observations highlight the importance of studying factors responsible for thrombosis in COVID-19 to imply suitable life-saving interventions.

VWF is a large multimeric prothrombic agent secreted by endothelial cells in response to systemic inflammation and also from platelets upon activation. It promotes platelet adherence, aggregation, and thrombosis (Ruggeri, 2007). The activity of VWF is regulated by A disintegrin and metalloproteinase with thrombospondin motifs-13 (ADAMTS13), which is a zinc-containing metalloprotease enzyme responsible for partial cleavage of ultra-large VWF multimers (>10,000 kDa) to high molecular weight multimers (<10,000 kDa) found in the circulation (X Zheng et al., 2001) (Fujikawa et al., 2001). The cleavage of ultra-large VWF multimers by ADAMTS13 depends on shear forces or platelet attachment to VWF exposing the ADAMTS13 cleavage site (Tripodi et al., 2008) (Peyvandi et al., 2010).

Under physiological conditions, the ultra-large VWF multimers are intrinsically active and can bind strongly with glycoprotein (GP) Ibα subunit of the GPIb-IX-V complex and promote platelet recruitment to the site of injury and hemostasis. However, cleaved VWF multimers undergo structural conformational changes to bury GP1bα binding domain within the VWF's core B-sheet and prevent platelet aggregation (Dong et al., 2002) (Valentijn & Eikenboom, 2013) (Choi et al., 2007) (Levy et al., 2001) (López & Dong, 2005) (Siedlecki et al., 1996) (Furlan, 1996).

During acute inflammation, injured endothelial cells release the ultra-large VWF multimers (Moake & Chow, 1998) (Sugita et al., 2013) (Rietveld et al., 2019) (Obermeier et al., 2019). When the released ultra-large VWF multimers exceed the proteolytic activity of ADAMTS13, it causes accumulation of ultra-large VWF multimers and contributes to thrombosis, affecting vital organs such as the brain, heart, and kidney (Furlan & Lämmle, 2001) (Feys et al., 2007) (Arya et al., 2002) (Sporn et al., 1986). Plasma ADAMTS13 activity deficiency (<10%) caused by ADAMTS13 gene mutations or autoantibodies against ADAMTS13 results in inherited or acquired TTP. ADAMTS13 activity can be normal or somewhat decreased (>20%) in other types of thrombotic microangiopathy. In addition, it has been demonstrated that ADAMTS13 deficiency is a risk factor for the development of myocardial infarction, stroke, cerebral malaria, and preeclampsia (X. L Zheng, 2015). COVID-19 causes a significant increase in VWF levels, which can surpass the capacity of ADAMTS13 to handle them, resulting in the production of large VWF multimers identical to TTP (Doevelaar et al., 2021). ADAMTS13 deficiency also causes ultra-large VWF multimers accumulation, leading to thrombocytopenia and microvascular thrombosis—a disorder called thrombotic thrombocytopenic purpura (TTP) (Doevelaar et al., 2021) (X. L Zheng, 2015). The majority of TTP adult patients showed decreased ADAMTS13 cleavage of ultra-large VWF multimers caused by the neutralization of ADAMTS13 by autoantibodies, usually of the immunoglobulin G (IgG) isotype, that leads to impaired ADAMTS13 function and acquired ADAMT13 activity deficiency (Furlan et al., 1998; Sarig, 2014; Tsai & Lian, 1998). The role of the reciprocal relationship between VWF and ADAMTS13 in thrombosis prevention and hemostasis maintenance is widely studied (Levi et al., 2018). Abnormal VWF/ADAMT13 ratio resulting from endothelial activation by inflammation was observed in ischemic stroke, myocardial infarction, cerebral malaria, sepsis, sickle cell disease, and arterial thrombosis (Gragnano et al., 2017) (Zander et al., 2015) (Ladeira et al., 2021) (Turner et al., 2006) (South & Lane, 2018) (Masias & Cataland, 2018).

The role of the interaction between VWF and ADAMTS13 in COVID-19 is not widely studied. Although studies report abnormal levels of ADAMTS13 among patients with COVID-19, these studies were mainly case reports with a small sample size. Also, they had not drawn enough explanation of the pathophysiology of CAC (Blasi et al., 2020) (Hayakawa et al., 2021).

Recently, several ADAMTS13 assays were developed to measure ADAMTS13 activity, antigen, or autoantibodies. These assays are useful for differentiation between congenital and acquired forms of TTP. In cases of acquired TTP, ADAMTS13 activity and ADAMTS13 antigens probably follow the same trend during the acute phase. Also, the measurement of ADAMTS13 activity could be a good predictor for the levels of ultra-large VWF and autoantibodies against ADAMTS13 in the plasma. However, ADAMTS13 antigen assays have less clinical utility in the cases of acquired TTP and the presence of autoantibodies, so they are not commonly used in clinical practice as they are considered quantitative and not functional assays (Starke et al., 2007) (Peyvandi et al., 2010).

ADAMTS13 activity test was considered based on the findings of initial studies from China, which reported abnormal coagulation parameters especially increased levels of fibrinogen, D-Dimer, decreased platelet count, thrombotic microangiopathies (TMA), pulmonary microvascular thrombosis, and TTP-like TMA (Tiwari et al., 2021).

TMA refers to a group of different diseases characterized by thrombocytopenia, hemolytic anemia, and microthrombosis. The main 2 prototypes of TMA are TTP and hemolytic uremic syndrome (HUS) (Saha et al., 2017). ADAMTS13 activity test is used for differential diagnosis between TTP and other forms of TMAs (Kremer Hovinga et al., 2017).

This study aimed to explore the potential role of ADAMTS13 activity in the pathophysiology of COVID-19 and investigated the relationship between ADAMTS13 activity and clinical manifestation, disease severity, and outcome.

Methods

Study Design and Study Population

This study is a noninterventional retrospective study of medical records of patients with COVID-19 treated in NMC Royal Hospital, Khalifa City, Abu Dhabi, UAE from April 8, 2020 to the end of March 2020.

Included patients were positive for SARS-CoV-2 as confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay by nasopharyngeal swabs under aseptic operation. Included patients in the study were hospitalized adult patients with COVID-19 aged 18 or above with different disease severity grades, who

had plasma ADAMTS13 activity test done, whereas those who did not undergo the test were excluded.

Patients identifiers were removed during data collection process, with complete protection of patients' privacy. This study was conducted according to the Declaration of Helsinki. The study was approved by the NMC Central scientific committee approval (NMCHC/CSC/2020/0033), NMC Regional Ethics committee (NMC/RREC/AUH/2020/0017), and Regional Research Ethics Committee, Department of Health, Abu Dhabi, UAE (DOH/CVDC/2020/2311).

SARS-CoV-2 Nasopharyngeal PCR test

RNA was extracted from the nasopharyngeal swabs using the Xybio extraction kit (Korea). RT-PCR was performed on the Bio-Rad Cycler PCR (USA) using Solgent's 2019-nCoV Real-Time Reverse Transcription PCR Kit, following the manufacturer's instructions. Viral detection was done using a CFX-96 plate reader obtained from Biorad in the United States. SARS-CoV-2 detection was performed using real-time reverse transcription polymerase chain reaction (RT-PCR) analysis of 2 target genes: the open reading frame 1ab (ORF1ab) and the nucleocapsid protein (N). This approach amplifies the genetic material present in the specimen and detects the presence of the virus. The sample's RNA is extracted and reverse transcribed to DNA. This DNA is utilized as a template for amplification, which is used to detect the presence of the virus. A cycle threshold value (Ct value) less than 40 was considered negative, and a CT value greater than 40 was considered positive.

Plasma Activity of ADAMTS13

The test was performed at the National Reference Laboratory (UAE) under order code (117913). ADAMT13 activity in the plasma was measured by liquid chromatography-tandem mass spectrometry (LC/MS-MS) assay. ADAMTS13 activity is determined based on its ability to cleave a synthetic polypeptide substrate (VWF73), which is added to the plasma samples. Synthetic VWF73 is a specific substrate of ADAMTS13 that consists of 73 amino acid residues from D1596 to R1668 of VWF. VWF73 also contains 2 important sites, which are the tyrosine-methionine cleavage site and another exosite responsible for the selective cleavage of ADAMTS13 (Kokame et al., 2004) (Crawley et al., 2011). Quantification of VWF73 proteolytic products is proportional to ADAMTS13 activity in the plasma samples (Hubbard et al., 2015). The cut-off value was of ADAMT13 activity was 66.8%; results exceeding this value were considered normal, whereas low ADAMTS13 activity was defined as results less than 66.8%. The test was developed by LabCorp Burlington, 1447 York Cort, Burlington, NC, USA.

Data Collection

Demographic and clinical data of all patients were obtained from the electronic medical records, and laboratory, radiological findings, therapeutic interventions, and disease outcomes were also extracted. Baseline laboratory tests were done at the time of and during admission, including complete blood count, C-reactive protein (CRP), D-Dimer, lactate dehydrogenase (LDH), liver function tests, kidney function tests, lymphocytic count, fibrinogen, and serum ferritin. Interleukin-6 (IL-6) test was done for some of them.

Serum IL-6 was measured in the National Reference Laboratory in UAE under order code (140916). IL-6 was detected in the serum using an enzyme-linked immunosorbent assay (ELISA); the normal range was 0.0–15.5 pg/ml. The test was developed by LabCorp Burlington, 1447 York Cort, Burlington, NC, USA.

All patients had chest X-ray and/or chest CT on presentation, and some of them had follow-up chest X-ray and/or chest CT within different interval times according to clinical assessment.

Prophylactic anticoagulation was advised in all severe cases and was increased to therapeutic levels in case of progressive deterioration and/or progressive increase in D-dimer test. The time interval between the first positive and the first negative PCR test of 2 consecutive negatives is defined as the time to viral clearance.

Statistical analysis

Continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were denoted as frequency (n) and percentage.

Chi-square test was used to investigate the correlation between ADAMTS13 activity and disease outcomes. The linear regression model was done to explore the correlation between ADAMTS13 activity and COVID-19 laboratory findings. The logistic regression model was used to determine the independent association of ADAMTS13 activity with different COVID-19 outcomes. The logistic regression model was also used to investigate the association between mortality and some COVID-19 laboratory findings, which were significant at the linear regression. We performed Kaplan-Meier survival analysis to investigate the time to viral clearance according to ADAMTS13 levels among patients with COVID-19.

Statistical analysis was done using R Software version 3.5.2 (2018-12-20) "Eggshell Igloo". A 2-sided p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of the Study Population

This study was a retrospective study on 87 mild to critical patients with COVID-19 who underwent plasma ADAMTS13 activity test in a private healthcare hospital (NMC Royal Hospital) in Abu Dhabi, UAE. The mean age of the patients with COVID-19 with low ADAMTS13 levels was 44.3 $\pm$ 8.2 years. In this study, 75 (86.2%) were males, and 71 (81.6%) were Asian. Baseline comorbidities presented in 48.3% of patients and included diabetes in 20 (22.98%) and hypertension in 17 (19.45%) patients. There were 68 (78.16%) patients with pneumonia based on the finding of X-ray and/or computerized tomography (CT) scan.

Pneumonia was observed in 38 (55.9%) of patients with low ADAMTS13 activity and 30 (44.1%) of patients with normal ADAMTS13 activity. There were 35 (40.23%) patients with severe disease symptoms and 6 (6.89%) deaths due to SARS-CoV-2 infection. Among patients included in our study, anticoagulants at prophylactic dose were administered to 9.2% and at a therapeutic dose to 33.3% of patients with COVID-19. Of the entire cohort, 42 (48.3%) reported lower levels of ADAMTS13, whereas 45 (51.7%) patients reported normal values of ADAMTS13. Detailed demographic and clinical characteristics were compared and shown in Table 1 and Table 2.

COVID-19 Patient's characteristics stratified by ADAMTS13 activity

Chi-square test was used to measure the association between ADAMT13 activity and different patient characteristics, including radiological findings, use of anticoagulants, disease severity, mortality, and the clinical presentations, as assessed by WHO ordinary scale for clinical improvement of COVID-19 (Table 2).

Among different laboratory findings, patients with COVID-19 with low ADAMTS13 activity had experienced significant increased levels of CRP, D-dimer, ALT, AST, fibrinogen, and ferritin ($p=0.001$, $p=0.016$, $p=0.039$, $p=0.007$, $p=0.004$, $p=0.005$, respectively) (Table 1).

Regarding the clinical outcomes, there was a statistically significant association between the low activity of ADAMT13 and the

Table 1
Patients characteristics data with COVID-19 stratified by ADAMTS13 activity. (Data are presented as mean and SD for continuous variables, and n and % for categorical variables).

Characteristics Age (years)	Mean (SD)	Low ADAMTS13 Activity (<67%)	Normal ADAMTS13 Activity (>67%)	*p*-Value
BMI (kg/m^2)	**Mean (SD)**	28.3 (3.9)	28.0 (5.3)	0.395
SEX	**Female**	5 (41.7%)	7 (58.3%)	0.622
	Male	37 (49.3%)	38 (50.7%)	
Race	**White**	4 (36.4%)	7 (63.6%)	0.438
	Asian	36 (50.7%)	35 (49.3%)	
	Black	1 (25.0%)	3 (75.0%)	
Patient characteristics				
HTN	**No**	32 (45.7%)	38 (54.3%)	0.332
	Yes	10 (58.8%)	7 (41.2%)	
DM	**No**	31 (46.3%)	36 (53.7%)	0.493
	Yes	11 (55.0%)	9 (45.0%)	
CVS	**No**	39 (47.6%)	43 (52.4%)	0.589
	Yes	3 (60.0%)	2 (40.0%)	
ANTICOAGULANTS	**Prophylactic**	7 (87.5%)	1 (12.5%)	<0.001
	Therapeutic	21 (72.4%)	8 (27.6%)	
	No	14 (28.0%)	36 (72.0%)	
CRP (mg/L)	**Median (IQR)**	66.5 (128.2)	19.0 (48.8)	0.001
D-Dimer (µg/mL)	**Median (IQR)**	0.8 (1.5)	0.4 (0.5)	0.016
LDH (u/l)	**Median (IQR)**	331.0 (249.0)	244.0 (150.0)	0.096
ALT (u/l)	**Median (IQR)**	49.0 (37.8)	40.0 (28.0)	0.039
AST (u/l)	**Median (IQR)**	49.5 (35.5)	38.0 (22.0)	0.007
Fibrinogen (mg/dL)	**Median (IQR)**	608.0 (266.8)	513.0 (260.0)	0.004
Ferritin (ng/mL)	**Median (IQR)**	756.5 (1276.1)	249.8 (480.4)	0.005
WBC ($\times 10^9$/L)	**Median (IQR)**	6.0 (3.0)	6.6 (2.8)	0.336
HB (g/dl)	**Median (IQR)**	13.9 (2.5)	14.0 (2.1)	0.794
Platelets ($\times 10^9$/L)	**Median (IQR)**	289.5 (254.5)	281.0 (121.0)	0.44
IL-6 (pg/mL)	**Median (IQR)**	43.8 (85.8)	58.1 (172.9)	0.641
Creatinine (µmol/L)	**Median (IQR)**	0.9 (0.2)	0.9 (0.2)	0.784
Neutrophil Count (%)	**Median (IQR)**	65.8 (25.3)	59.1 (18.9)	0.09
Lymphocyte Count (%)	**Median (IQR)**	23.3 (20.9)	28.1 (15.5)	0.232
NLR	**Median (IQR)**	2.8 (4.1)	2.1 (2.1)	0.191
RDW.CV (%)	**Median (IQR)**	13.1 (1.1)	12.9 (1.1)	0.153
Blood	**A**	9 (45.0%)	11 (55.0%)	0.766
Group	**B**	8 (57.1%)	6 (42.9%)	
	O	10 (43.5%)	13 (56.5%)	
	AB	2 (66.7%)	1 (33.3%)	
RH	**Positive**	23 (47.9%)	25 (52.1%)	0.172
	Negative	4 (80.0%)	1 (20.0%)	
PT (Seconds)	**Median (IQR)**	14.0 (2.0)	13.0 (1.5)	0.342
INR	**Median (IQR)**	1.0 (0.2)	1.0 (0.1)	0.539

Abbreviations: ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: Body Mass Index, CRP: C Reactive protein, CVS: Cardiovascular diseases, DM: Diabetes Mellitus, HB: hemoglobin, HIN: hypertension, IL-6: interleukin 6, INR: International normalized ratio, LDH: lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, PT: prothrombin time, RDW: Red cell distribution width, RH: Resus Factor, WBC: White blood cells.

radiological findings done at the time of admission. There were 38 (55.9%) patients with pneumonia in low ADAMT13 treatment groups (p=0.007) (Table 2).

Patients with severe COVID-19 were more likely in the low ADAMT13 activity group (61.9%) than the normal activity group (20%) (p <0.001). These findings were also observed by WHO ordinary scale that showed more mild and moderate cases with normal ADAMT13 activity, whereas more severe cases (scale from 4–7) with low activity (p=0.012). ICU admission and mechanical ventilation rates were increased significantly in the low ADAMTS13 group (p=0.046, p=0.018, respectively). Death was more frequently observed among patients (5 patients, 11.9%) with low ADAMTS13 activity than those with normal activity (1 patient, 2.2%); however, the correlation between mortality and ADAMTS13 level was not significant (p=0.075) (Table 2).

Logistic Regression Analysis

We further investigated the independent association of ADAMTS13 levels and different disease outcomes among patients with COVID-19. The logistic regression model revealed that the risk of pneumonia (Figure 1), severe disease outcomes (Figure 2), need for mechanical ventilation (Figure 3), and use of anticoagulants (Figure 4) had been increased significantly among patients with low ADAMTS13 activity by 4.75 folds, 6.50 folds, 4.1 folds, and 8 folds, respectively, than patients with normal ADAMTS13 activity (OR= 4.75, 95% CI: [1.54-18.02], p=0.011), (OR= 6.50, 95% CI: [2.57-17.74], p<0.001), (OR= 4.10, 95% CI: [1.29-15.82], p=0.024), (OR=8.00, 95% CI: (3.13-22.16), p<0.001), respectively) (Table 3).

Although the risk of mortality and ICU admission also increased among patients with COVID-19 with low levels of ADAMTS13 by 5.95 and 3.82 nonsignificantly (OR= 5.95, 95% CI: [0.91-116.64], p=0.111), (OR= 3.82, 95% CI: [1.05-18.24], p=0.058, respectively) (Table 3).

Initial laboratory parameter and ADAMTS13 activity

The linear regression model was done to investigate the correlation between ADAMTS13 level and laboratory findings of patients with COVID-19. There was a statistically significant correlation between elevated levels of CRP, AST, fibrinogen, and ferritin and decreasing ADAMTS13 levels by about 0.13, 0.16, 0.04, and 0.0044 decrease (p<0.001, p=0.026, p=0.001, p=0.010, respectively) (Table 4).

Table 2
Univariate comparative analysis for COVID-19 outcomes in relation to ADAMTS13 Activity (Data are presented as n and %).

COVID-19 outcomes		Low ADAMTS13 Activity(<67%)	Normal ADAMTS13 Activity(>67%)	P value
Radiology	**Normal**	4 (21.1%)	15 (78.9%)	0.007
	Pneumonia	38 (55.9%)	30 (44.1%)	
Mortality	**Alive**	37 (45.7%)	44 (54.3%)	0.075
	Dead	5 (83.3%)	1 (16.7%)	
WHO Ordinary	**2**	5 (26.3%)	14 (73.7%)	0.012
Scale	**3**	12 (35.3%)	22 (64.7%)	
	4	10 (66.7%)	5 (33.3%)	
	5	8 (72.7%)	3 (27.3%)	
	6	1 (100.0%)	0 (0.0%)	
	7	5 (83.3%)	1 (16.7%)	
Severity	**Non Severe**	16 (30.8%)	36 (69.2%)	<0.001
	Severe	26 (74.3%)	9 (25.7%)	
ICU Admission	**No**	33 (44.0%)	42 (56.0%)	0.046
	Yes	9 (75.0%)	3 (25.0%)	
Ventilation(invasive/non –invasive)	**No**	30 (42.3%)	41 (57.7%)	0.018
	Yes	12 (75.0%)	4 (25.0%)	

Abbreviations: ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, ICU: intensive care unit.

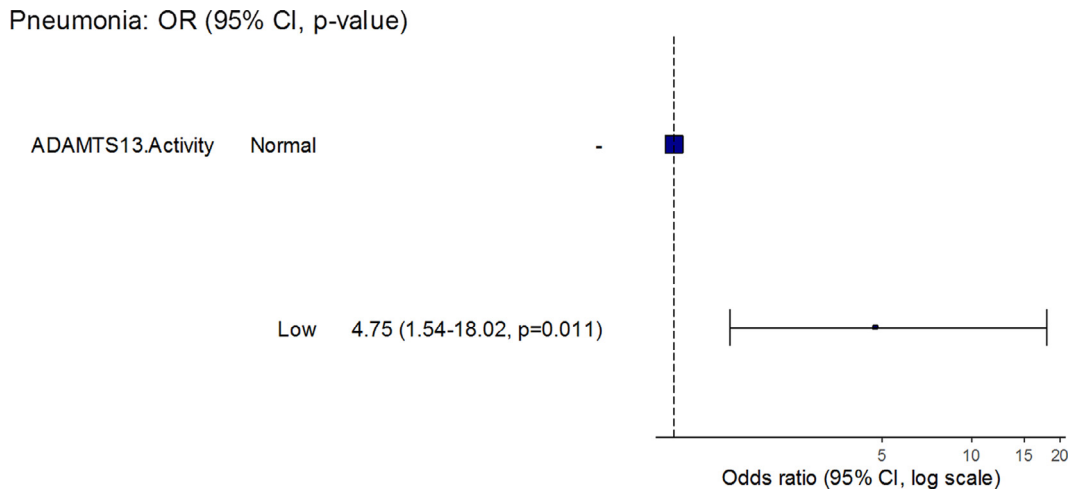

Figure 1. Forrest Plot of the Odds of Pneumonia Based on ADAMTS13 Level, showing risk of pneumonia had been increased significantly among patients with ADAMTS13 deficiency by 4.75 folds than patients with normal ADAMTS13 activity (OR= 4.75, 95% CI: [1.54-18.02].

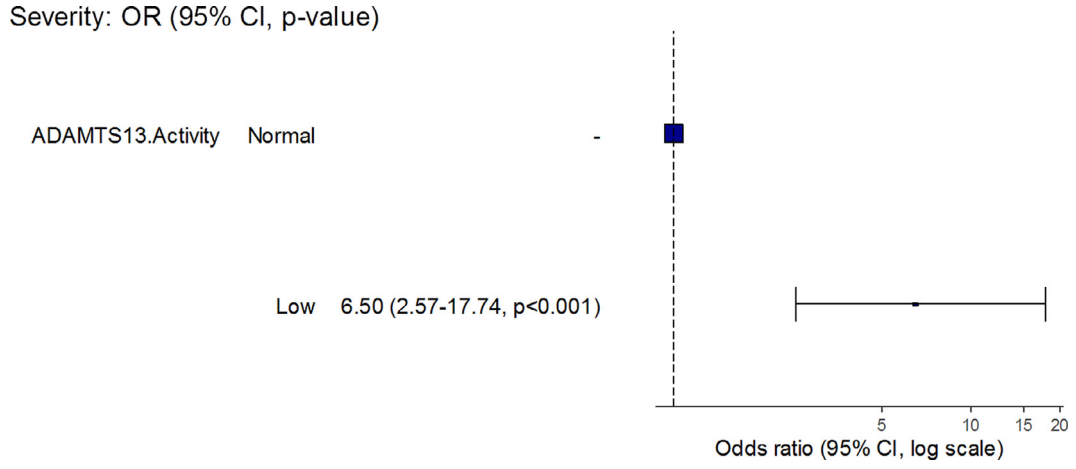

Figure 2. Forrest Plot of the Odds of Severity of COVID-19 Based on ADAMTS13 Level showed severity outcome had been increased significantly among patients with ADAMTS13 deficiency by 6.50 folds than patients with normal ADAMTS13 activity (OR = 6.50, 95% CI: [2.57-17.74], p<0.001).

Patient's characteristics stratified by mortality outcome

To further understand prognostic factors associated with COVID-19, we conducted logistic regression analysis to investigate the association between mortality and some COVID-19 laboratory findings, which were significant at linear regression.

We found that the risk of mortality increased by 14% for each 1-year increase in patient age (OR=1.14, 95% CI: [1.04-1.30], p=0.015). The risk of mortality due to COVID-19 also increased significantly by 50%, 1%, 1%, and 0.05% increase for each 1-unit increase in D-dimer, LDH, fibrinogen, and ferritin respectively (OR=1.50, 95% CI: [1.24-2.04], p=0.001), (OR=1.01, 95% CI: [1.00-1.01], p=0.004),

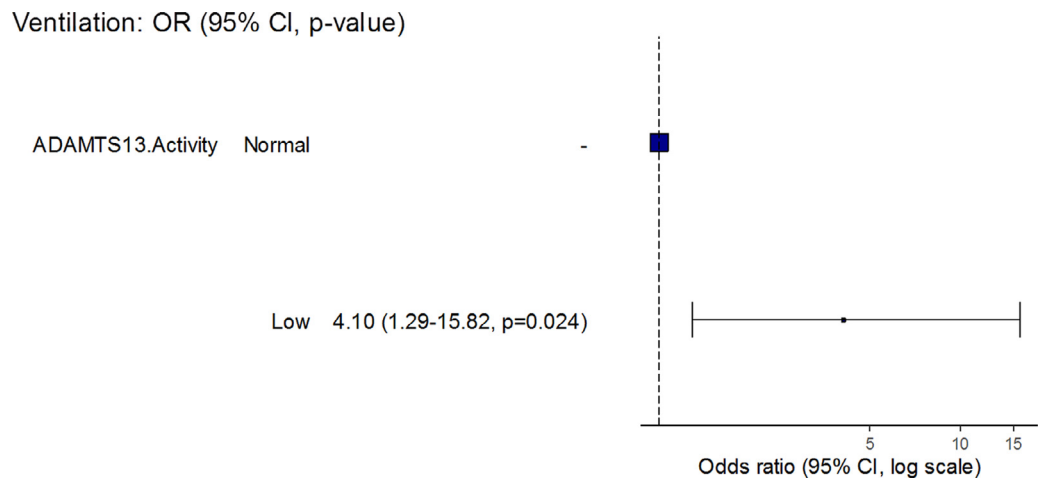

Figure 3. Forrest Plot of the Odds of Need for Mechanical Ventilation Based on ADAMTS13 Level showed that it had been increased significantly among patients with ADAMTS13 deficiency by 4.1 folds than patients with normal ADAMTS13 activity (OR = 4.10, 95% CI: [1.29-15.82], p=0.024).

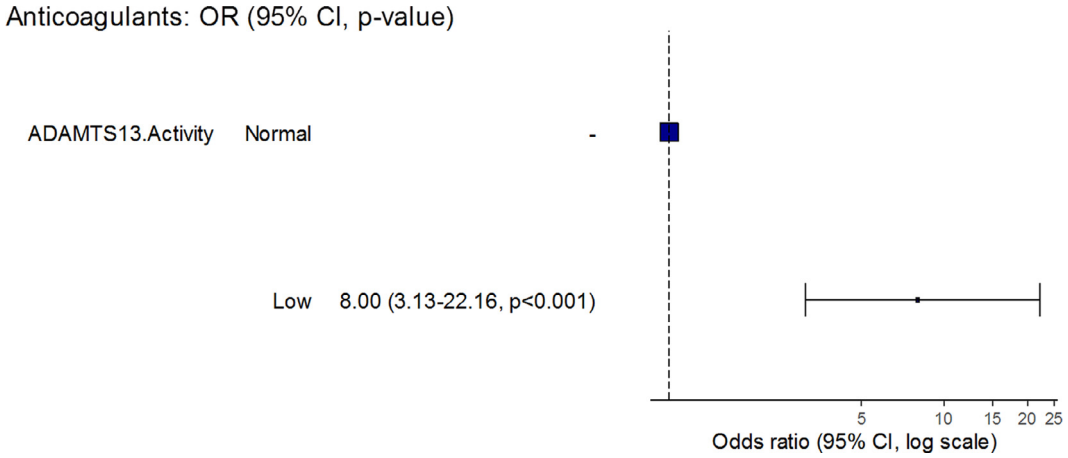

Figure 4. Forrest Plot of the Odds of Anticoagulants use Based on ADAMTS13 Level showed that the use of anticoagulants had been increased significantly among patients with ADAMTS13 deficiency by 8-fold than normal ADAMTS13 activity patients (OR=8.00, 95% CI: (3.13-22.16), p<0.001).

Table 3
Logistic regression models to investigate the association between Low ADAMTS13 Activity and COVID-19 outcomes

COVID-19 outcomes	Low ADAMTS13 ActivityOR (95% CI)	P value
Pneumonia	4.75 [1.54-18.02]	0.011
Mortality	5.95 [0.91-116.64]	0.111
Severity	6.50 [2.57-17.74]	<0.001
ICU Admission	3.82 [1.05-18.24]	0.058
Ventilation (invasive/noninvasive)	4.10 [1.29-15.82]	0.024
Anti-coagulants	8.00 [3.13-22.16]	<0.001

(OR=1.01, 95% CI: [1.00-1.01], p=0.011), (OR=1.0005, 95% CI: [1.00-1.00], p= 0.015), respectively) (Table 5).

In contrast, we could not find a statistically significant association between mortality and ADAMTS13 levels (p=0.194), CRP (p=0.127), ALT (p=0.696), AST (p=0.495), or IL-6 (p=0.055).

ADAMTS13 activity and time to viral clearance

Kaplan-Meier curve revealed that ADAMTS13 activity was not significantly associated with the median time to viral clearance in patients with COVID-19 during the comparison between patients with low ADAMTS13 activity to those with normal activity (20 days, 95% CI: [16-27] days, vs. 17 days, 95% CI: [13-22] days, p=0.08, Log rank= 3.1) (Figure 5). Other confounding factors could have accounted for the longer median time to viral clearance observed among patients with low ADAMTS13 activity.

Discussion

In this retrospective study, we aimed to investigate the potential role of ADAMTS13 activity in the pathophysiology of COVID-19. We found that low ADAMT13 activity was significantly associated with radiological findings of pneumonia, more severe disease course, ICU admission, need for mechanical ventilation, and use of anticoagulants. The time to viral clearance was longer in patients with low ADAMTS13 activity; however, the survival analyses revealed that this difference was not significant. There was no association between ADAMTS13 activity and age, gender, or presence of comorbidities. The mortality rate was higher in the low

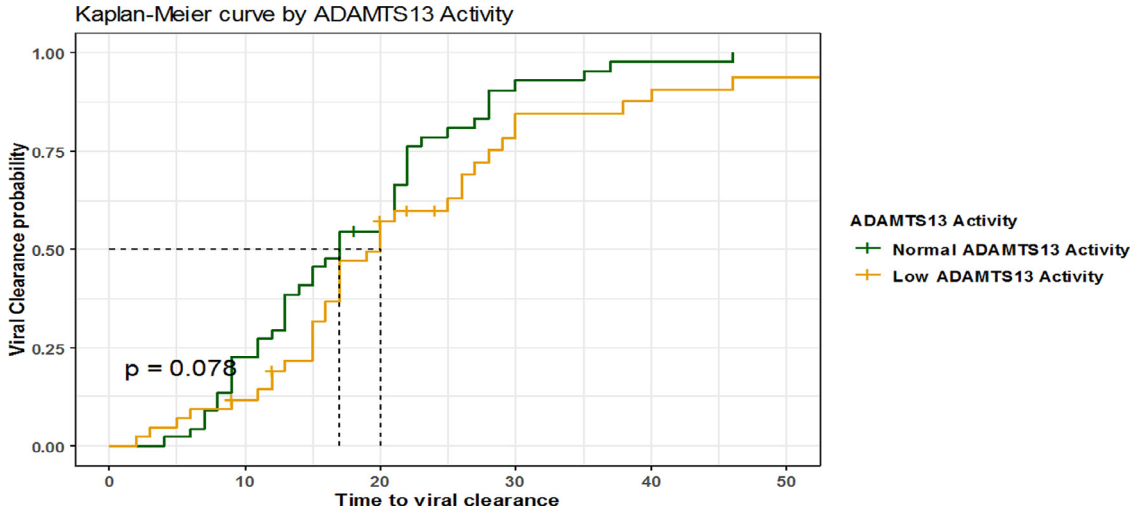

Figure 5. Kaplan-Meier Curve of the Association of Time to Viral Clearance and ADAMT13 Activity showed nonsignificantly longer median time to viral clearance in patients with COVID-19 with low ADAMTS13 level than those with normal ADAMTS13 activity (20 days, 95% CI: [16-27] days, vs. 17 days, 95% CI: [13-22] days, p=0.08, Log rank= 3.1).

Table 4
Linear regression models to investigate the correlation between Low ADAMTS13 Activity and COVID-19 laboratory findings.

Lab. Findings	Low ADAMTS13 ActivityCoefficient (95% CI)	P value
CRP (mg/L)	-0.13 (-0.20 to -0.07)	<0.001
D-Dimer (µg/mL)	-0.73 (-1.77 to 0.30)	0.163
LDH (u/l)	-0.01 (-0.03 to 0.00)	0.074
ALT (u/l)	-0.10 (-0.24 to 0.05)	0.188
AST (u/l)	-0.16 (-0.30 to -0.02)	0.026
Fibrinogen (mg/dL)	-0.04 (-0.06 to -0.02)	0.001
Ferritin (ng/mL)	-0.0044 (-0.01 to -0.00)	0.010
WBC ($\times 10^9$/L)	0.57 (-1.46 to 2.60)	0.577
HB (g/dl)	-0.45 (-1.67 to 0.77)	0.466
Platelets ($\times 10^9$/L)	-0.03 (-0.06 to 0.01)	0.107
IL-6 (pg/mL)	-0.00 (-0.02 to 0.01)	0.593
Creatinine (µmol/L)	-7.57 (-15.58 to 0.43)	0.063
Neutrophil Count (%)	-0.26 (-0.57 to 0.06)	0.110
Lymphocyte Count (%)	0.21 (-0.17 to 0.59)	0.275
NLR	-0.98 (-2.11 to 0.14)	0.085
RDW.CV (%)	-2.08 (-4.44 to 0.28)	0.083
Blood Group	-1.45 (-7.29 to 4.39)	0.621
RH	-6.95 (-27.76 to 13.86)	0.506
PT (Seconds)	-3.02 (-8.19 to 2.15)	0.244
INR	-6.45 (-33.86 to 20.97)	0.641

Abbreviations: ALT: The alanine aminotransferase, AST: aspartate aminotransferase, CRP: C Reactive protein, HB: hemoglobin, IL-6: interleukin 6, INR: International normalized ratio, LDH: lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, PT: prothrombin time, RDW: Red cell distribution width, RH: Resus Factor, WBC: White blood cells.

ADAMTS13 group but did not reach a statistically significant level. The VWF/ADAMTS13 axis is poorly studied in COVID-19; this report is considered one of the earlier studies that explored the effect of altered ADAMTS13 activity among patients with COVID-19.

Here, the frequency of death was more frequent among patients with low ADAMTS13 levels despite the lack of a statistically significant association between mortality of COVID-19 and low ADAMT13 activity; this finding is in contrast to the results of some other studies (Tiscia et al., 2020) (Sweeney et al., 2021) (Rodríguez et al., 2021). This difference could be due to different patient characteristics and/or the different anticoagulation doses used in different studies. Furthermore, the small sample size in all studies could impact the interpretation.

The definite mechanism of abnormal VWF/ADAMTS13 axis contribution to disease progression and mortality is not well understood. Meijenfeldt et al. reported that low ADAMT13 levels were associated with the need for mechanical ventilation of COVID-19, which is consistent with our findings. Meanwhile, they reported that mortality was associated with decreased ADAMTS13 activity, which is in contrast with our results (von Meijenfeldt et al., 2021). Dushianthan et al. also reported that ADAMTS13 deficiency was associated with an increased risk for mechanical ventilation by 7.57, which is comparable to our findings (Dushianthan et al., 2021). Here, the frequency of death was more frequent among patients with low ADAMTS13 levels despite that we could not find a statis-

Table 5
Logistic regression models to investigate the association between mortality and some COVID-19 laboratory findings which were significant at linear regression. (Data are presented as mean and SD)

Lab. Findings		Alive	Dead	OR (95% CI)	P value
Age (Years)	**Mean (SD)**	42.5 (9.8)	53.8 (8.4)	1.14 (1.04-1.30)	0.015
ADAMTS13 Activity (%)	**Mean (SD)**	69.1 (20.7)	57.6 (17.2)	0.97 (0.93-1.01)	0.194
CRP (mg/L)	**Mean (SD)**	55.5 (62.9)	97.3 (40.2)	1.01 (1.00-1.02)	0.127
D-Dimer (µg/mL)	**Mean (SD)**	1.1 (2.4)	13.8 (5.3)	1.50 (1.24-2.04)	0.001
LDH (u/l)	**Mean (SD)**	302.2 (150.3)	990.8 (890.1)	1.01 (1.00-1.01)	0.004
ALT (u/l)	**Mean (SD)**	50.1 (31.4)	44.6 (19.8)	0.99 (0.95-1.02)	0.696
AST (u/l)	**Mean (SD)**	48.1 (31.6)	58.0 (20.4)	1.01 (0.98-1.03)	0.495
Fibrinogen (mg/dL)	**Mean (SD)**	529.2 (189.7)	763.2 (160.0)	1.01 (1.00-1.01)	0.011
Ferritin (ng/mL)	**Mean (SD)**	679.3 (1066.5)	2616.3 (2469.0)	1.0005(1.00-1.00)	0.015
IL-6 (pg/mL)	**Mean (SD)**	192.4 (418.9)	1199.8 (1380.6)	1.00 (1.00-1.00)	0.055

Abbreviations: ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C Reactive protein, IL-6: interleukin 6, LDH: lactate dehydrogenase.

tically significant association between mortality of COVID-19 and low ADAMT13 activity; this finding is in contrast to the results of some other studies (Tiscia et al., 2020) (Sweeney et al., 2021) (Rodríguez et al., 2021). This difference could be due to different patient characteristics and/or the different anticoagulation doses used in different studies. Furthermore, the small sample size in all studies could impact the interpretation.

Several variables were recognized as a risk factor for poor outcomes of COVID-19. Male gender, older age, obesity, and comorbidities such as acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, smoking, and increased D-dimer are all distinct patient characteristics associated with risk of fatal COVID-19 outcomes (Dessie and Zewotir, 2021).

In severe COVID-19, the appropriate anticoagulation strategy is still debatable. COVID-19 may be profoundly hypercoagulable before anticoagulant therapy; yet, bleeding complications have also been documented. In COVID-19 nonsurvivors, von Meijenfeldt et al. found that markers of in vivo coagulation and fibrinolysis were higher in patients who received higher levels of care. Ex vivo thrombin production was also higher in patients in general wards and similar in patients in higher levels of care despite higher LMWH dosages in patients in higher levels of care (von Meijenfeldt et al., 2021).

In our study, anticoagulant therapy was recommended for all patients with severe COVID-19, and the doses of anticoagulants were increased to therapeutic levels if further deterioration was observed. In addition, we observed a substantial link between ADMATS13 activity and anticoagulant use. This leads us to believe that early initiating and increasing anticoagulation to therapeutic levels in deteriorating patients with severe COVID-19 may avert deteriorating conditions and minimize the need for ICU admission and mechanical ventilation.

According to the linear regression model, we could not find an association between D-dimer concentration and ADAMTS13 activity; this was in opposition to Tiscia et al. who reported an independent association between D-dimer concentration at admission ($P = 0.0145$) and age ($P= 0.0036$) and ADAMTS13 activity levels (Tiscia et al., 2020). This difference could be attributed to different patient characteristics in both studies. COVID-19 infection is associated with exaggerated immune response, activated macrophages, and release of several proinflammatory cytokines, including TNF-α, IL-6, IL-8, and IL-1β. Furthermore, the interaction between viral S protein and ACE-2 could activate platelets and enhance their inflammatory response and prothrombic action (Argañaraz et al., 2020).

Two mechanisms can facilitate thromboembolic manifestations. First, by the passage of different proinflammatory mediators generated in pulmonary tissue to the blood, inflammatory mediators such as IL-6 and TNF-α activates endothelial cells facilitate platelet and monocytes aggregation and increase the expression of tissue factor (TF) glycoprotein, which in turn will trigger the coagulation cascade leading to thrombus formation. The second mechanism is mediated by decreased ADAMTS13 activity by the inhibitory effect of proinflammatory mediators such as C-reactive protein, IL-6, IL-1β, and VWF accumulation in the plasma (Argañaraz et al., 2020).

Several studies showed that COVID-19 with microangiopathy had an abnormal ADAMTS13/VWF ratio; although, Escher et al. reported no association of ADAMTS13 activity and microangiopathy in patients with COVID-19 (Martinelli et al., 2020) (Pascreau et al., 2021) (Escher et al., 2020). However, Nazy et al. reported that ADAMTS13 activity was not severely impaired among critically ill patients with COVID-19, and increased VWF/ADAMTS13 ratio is more likely secondary to microthrombotic complications compounded with platelet-activating immune complexes (Nazy et al., 2021).

The cytokine storm is the hallmark of severe COVID-19 pathogenesis, and previous research has revealed that inflammatory cytokines activate the endothelium, resulting in the exocytosis of endothelial WBPs and consequently VWF (Chen J et al., 2018). In the present 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. The association between increasing COVID-19 severity and low ADAMT13 activity was also confirmed by other studies (Ward et al., 2021) (Rovas et al., 2021). Increased VWF in the plasma is usually accompanied with decreased levels of ADAMT13 due to its consumption while cleaving ultra-large VWF multimers (Philippe et al., 2021).

Doevelaar et al. had reported the absence of ADAMT13 deficiency among COVID-19 cases included in their study; however, there was a significant decrease in ADAMTS13/VWF antigen ratio. This was explained by the production of excess VMF that exceeded the proteolytic capacity of ADAMTS13, resulting in its deficiency (Doevelaar et al., 2021). Meanwhile, Bashir and her colleagues proposed that increased secretion of VWF and decreased ADAMT13 activity could be mediated by hyperferritinemia, consequently inducing pathologic immune activation, thrombosis, and organ damage (Bashir et al., 2021).

It was demonstrated that mortality is significantly associated with IL-6 levels (Ruan et al., 2020). Notwithstanding that in our study, IL-6 was not related to mortality or ADAMTS13 deficiency, whereas AST and ALT were significantly associated with low ADAMTS13 activity, but most patients had normal or mildly increased laboratory findings. However, IL-6 was measured in a few patients, which could affect the accuracy of these findings, but that could also suggest that ADAMT13 activity is less likely to be low due to its inhibition by IL-6 or impaired production but mostly could be due to its consumption while cleaving VWF (X Zheng et al., 2002) (Bernardo et al., 2004).

Another explanation is proposed by Henry et al. who reported complement system hyperactivation characterized by a significant increase of C3a, C3a/C3 and sC5b-9/C3 ratios, and induction of inflammation, endothelial damage, and coagulation among patients with severe COVID-19 (Henry et al., 2021). They also reported a negative correlation with ADAMTS13 activity, suggesting the role of complement system hyperactivation and ADAMTS13 deficiency in CAC (Henry et al., 2021).

Hyperinflammation and procoagulation were observed among patients with COVID-19, suggesting a harmful effect of SARS-CoV-2 on endothelial cells. Endothelial damage may be provoked by various mechanisms directly by binding the virus to endothelial cells and promoting cell apoptosis or indirectly through binding Ang II to A1T receptor on endothelial cells, promoting coagulopathy, microvascular thrombosis, and hypofibrinolysis (Iwasaki et al., 2021). Accumulation of Ang II in the lungs is also associated with enhanced plasminogen activator inhibitor-1 (PAI-1) genetic expression. PAI-1 promotes thrombosis and inhibits fibrinolysis by inhibition of urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA), leading to vascular microthrombosis in patients with COVID-19 (Bernard et al., 2021).

Endothelial cells of patients with severe COVID-19 can be activated by elevated proinflammatory cytokines such as IL-6 and TNF-α. Elevated VMF with reduction of ADAMT13 activity was detected among ICU-admitted patients and associated with thrombotic microangiopathy (Bonaventura et al., 2021). Pericytes apoptosis mediated by SARS-CoV-2 is also suggested in microvascular dysfunction and coagulability caused by COVID-19 (Evans et al., 2020).

Here, we also demonstrated for the first time that the time to viral clearance is longer among patients with low ADAMTS13 activity despite being not significant, which could be explained by the sample size limitation and the role of confounding factors

among presented patients. This could correspond to increased risk of disease severity, coagulation, and recovery among patients with COVID-19 with low ADAMTS13 levels and highlight the importance of studying the virologic response in the presence of abnormal coagulation biomarkers for better prognosis of patients with COVID-19.

An experimental study studied the role of ADAMTS13 and recombinant ADAMTS13 (rADAMTS13) in mice with intracerebral hemorrhage (ICH)–induced brain injury and found that rADAMTS13 was associated with decreased levels of different chemokines and cytokines such as IL-6 and reduced activation of neutrophils and microglial cells. The anti-inflammatory and brain-protective effect of rADAMTS13 was reversed by rVWF (Cai et al., 2015). These findings emphasize the importance of rADAMTS13 in regulating pathological inflammation and coagulation. Furthermore, rADAMTS13 could be suggested as a potential treatment for severe COVID-19 to facilitate the degradation of ultra-large VWF and correct an imbalanced ADAMTS13/VMF axis.

In our study, patients with lower ADAMTS13 activity were more frequently admitted to the ICU than those with normal activity, but the correlation was not statistically significant. This observation could be related to the early and upgrading use of anticoagulation in severe cases. Plasma exchange with ADAMT13 replacement could be beneficial in patients with COVID-19 to provide passive immunity, treat possible TTP and ADAMT13 deficiency, and remove inflammatory cytokines (Furlan M, Robles R, Morselli B, Sandoz P, 1999) (Tanne, 2020).

These findings suggest the beneficial prognostic value of measuring ADAMT13 activity to predict disease severity and outcomes. It is recommended to measure ADAMT13 and VWF during the diagnosis of patients with COVID-19 with suspected microangiopathy.

The limitations of our study include possible bias and intrinsic confounders; this was a retrospective study that could only study the correlation but not the causation, so larger randomized clinical trials are needed to investigate the causal relationship between ADAMTS13 activity and COVID-19. Another limitation is that the male gender was more dominant, affecting the interpretation of our results, as previous studies showed that the male gender is associated with more severe COVID-19 outcomes. We also recommend the measurement of different complement proteins and cytokines, which could have a vital role in altering the VWF/ADAMTS13 axis.

Conclusion

In conclusion, throughout the study of the relationship between ADAMTS13 activity and COVID-19 pathophysiology, presentation, severity, and mortality, we observed a link between low ADAMTS13 activity and the development of pneumonia, the severity of COVID-19, need for mechanical ventilation, and the use of anticoagulants. Whereas there was no significant link between mortality and ADAMTS13 levels, more research is required to determine the prognostic value of the VWF/ADAMTS13 axis in patients with COVID-19. Furthermore, we believe that rADAMTS13 could provide a novel therapeutic strategy for severe COVID-19.

Conflict of Interest

The authors have no conflict of interest to declare.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the NMC Central scientific committee (NMCHC/CSC/2020/0033), NMC Regional Ethics committee (NMC/RREC/AUH/2020/0017), and Regional Research Ethics Committee, department of health, Abu Dhabi, UAE number (DOH/CVDC/2020/2311).

Informed Consent Statement

This is a retrospective study; all patient identifiers were removed during the data collection process, with complete protection of the patients' privacy. This study was conducted according to the Declaration of Helsinki and approved by the IRB of the NMC Central scientific committee (NMCHC/CSC/2020/0033), NMC Regional Ethics committee (NMC/RREC/AUH/2020/0017), and Regional Research Ethics Committee, Department of Health, Abu Dhabi, UAE number (DOH/CVDC/2020/2311).

Data Availability Statement

Data are available upon request from the first and corresponding author

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.019.

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