

Increased VWF and Decreased ADAMTS-13 in COVID-19: Creating a Milieu for (Micro)Thrombosis

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Abstract

von Willebrand factor (VWF) is a large adhesive multimeric protein involved in hemostasis. The larger the size (or number of VWF multimers), the greater the functionality of the protein. A deficiency or defect of VWF can lead to von Willebrand disease (VWD) and cause bleeding. Conversely, an increase in VWF may create an environment that promotes thrombosis. ADAMTS-13 (*a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13*), sometimes called VWF-cleaving protease, is primarily responsible for controlling the size of VWF. The most severe deficiency (<10% of normal levels) of ADAMTS-13 arises in thrombotic thrombocytopenic purpura, a condition characterized by the presence of ultralarge VWF and clinically resulting in enhanced risk of thrombosis. However, ADAMTS-13 deficiency may result from other pathological processes. Of relevance is the recent finding that COVID-19 (coronavirus disease 2019) is associated with both increased levels and activity of VWF as well as generally decreased (or occasionally normal) activity levels of ADAMTS-13. Thus, in COVID-19 there is an alteration in the VWF/ADAMTS-13 axis, most often described by increased VWF/ADAMTS-13 ratio (or reduced ADAMTS-13/VWF ratio). COVID-19 is also associated with high prothrombotic risk. Thus, the imbalance of VWF and ADAMTS-13 in COVID-19 may be providing a milieu that promotes (micro) thrombosis, in a clinical picture resembling a secondary thrombotic microangiopathy in some patients. This review therefore assesses the literature on VWF, ADAMTS-13, and COVID-19. Whenever reported in COVID-19, VWF has always been identified as raised (compared with normal reference ranges or control populations). Reports have included VWF level (i.e., VWF antigen) and in some cases one or more VWF “activity” (e.g., collagen binding; platelet glycoprotein Ib [GPIb] binding, using ristocetin cofactor or more modern versions including VWF:GPIbR [recombinant] and VWF:GPIbM [mutant]). Whenever reported, ADAMTS-13 has been reported as “normal” or reduced; however, it should be recognized that “normal” levels may still identify a relative reduction in individual cases. Some reports also discuss the raised VWF/ADAMTS-13 (or reduced ADAMTS-13/VWF) ratio, but very few provide actual numerical data.

Keywords

- ▶ von Willebrand factor
- ▶ ADAMTS-13
- ▶ COVID-19
- ▶ thrombosis

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von Willebrand factor (VWF) is a large adhesive multimeric protein involved in hemostasis. The larger the size (or number of VWF multimers), the greater the functionality of the protein.¹ A deficiency or defect of VWF can lead to von Willebrand disease (VWD) and cause bleeding.² Conversely, an increase in VWF may cause thrombosis.³ Although an increase in VWF per se may be associated with thrombosis, it is an increase in the larger VWF protein moieties (sometimes called high-molecular-weight [HMW] VWF) that are more likely to provide a milieu conducive to thrombosis. The VWF cleaving protease ADAMTS-13 (*a* disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is primarily responsible for controlling the size of plasma VWF, as this enzyme proteolytically cleaves VWF multimers into smaller moieties, less able to promote thrombus formation.⁴

The most severe deficiency of ADAMTS-13 arises in thrombotic thrombocytopenic purpura (TTP),⁴ a disorder characterized by levels of ADAMTS-13 less than 10% of normal, with consequent occurrence of ultralarge forms of VWF. Not unsurprising, then, is that thrombosis is a key feature of TTP. However, a relative ADAMTS-13 deficiency can arise in a variety of pathophysiological states, including secondary microangiopathies.⁵

Most relevant for this review is that recent evidence has emerged that COVID-19 (coronavirus disease 2019), which is often associated with a high thrombotic risk, is characterized in many patients as an imbalance in the VWF/ADAMTS-13 “axis,” in a clinical picture reported to closely resemble a secondary thrombotic microangiopathy.⁶ In summary, the most seriously affected patients with COVID-19 express a relatively high VWF/ADAMTS-13 ratio, which may thus create a milieu that promotes (micro)thrombosis. The current narrative review thus discusses findings reported to date regarding levels and activity of VWF and ADAMTS-13 in COVID-19.

Methods

We felt that a narrative review would suit our purpose best. The PubMed database (<https://pubmed.ncbi.nlm.nih.gov>) was therefore searched using various iterations of COVID-19 together with various iterations of ADAMTS-13 and VWF. An initial search was later updated to be current as of February 15, 2021. Of 100 total hits, we then excluded reviews, commentaries, single case reports, and articles found to be irrelevant to the topic, to achieve a core set of 38 articles that identified levels of VWF protein (VWF antigen [VWF:Ag]) and in some cases VWF “activity” and 22 articles that identified levels of ADAMTS-13 activity. Notably, 18 articles reported on VWF in COVID-19 (total = 1,324 COVID-19 patients),^{7–24} 2 reported on ADAMTS-13 and COVID-19 (total = 36 COVID-19 patients),^{25,26} and 20 reported on both VWF and ADAMTS-13 in COVID-19 (total = 1,197 COVID-19 patients)^{27–47} (► **Tables 1–3**). Thus, data were available for VWF on more than 2,500 COVID-19 patients, and for ADAMTS-13 on more than 1,100 COVID-19 patients. VWF activity was reported as a variety of “activities,” including

VWF:CB (collagen binding), VWF:RCo (ristocetin cofactor), VWF:GPIbR (glycoprotein Ib, recombinant), and VWF:GPIbM (glycoprotein Ib, mutant). In some articles, other “activities” were described, and in some reports VWF “activity” assays were otherwise unspecified (► **Tables 1 and 2**). We restricted numerical reporting to studies containing more than five COVID-19 cases.

VWF Level and Activity in COVID-19

Most reports provided values for only VWF:Ag, albeit using a wide variety of methods (► **Tables 1 and 2**). Fewer reports provided values for VWF “activity,” with a wide range of different activities reported; these in turn were also assessed using a wide variety of methods, sometimes unspecified (► **Tables 1 and 2**). When reported, VWF:Ag and various VWF activities were invariably increased compared with normal reference ranges (NRRs) or control groups (► **Tables 1 and 2**). A few reports also provided values in different stages or severities of COVID-19. In general, higher levels of VWF:Ag or VWF activity were associated with more severe cases and nonsurvival.

VWF:Ag

► **Figure 1A** summarizes reports identifying the level of VWF:Ag in cases of COVID-19 compared with NRRs or controls, where more than five cases of COVID-19 were reported. Of interest, although the expected NRR for VWF:Ag would approximate 50 to 200 U/dL (or % of normal), the literature on COVID-19 matches the general literature on VWF, and the reported NRR varied widely based on the individual study (and thus the methodology used; ► **Fig. 1A**). Nevertheless, in general, the upper limit of normal was below 200 U/dL (or %). In all studies, comprising various cohorts of COVID-19 patients, the reported median values among infected patients were always well above 200 U/dL, and, indeed, so too were most of the reported lower limits of interquartile range (IQR) or standard deviation (SD) values (► **Fig. 1A**).

► **Figure 1(B–D)** shows additional data on VWF:Ag in COVID-19, where reports investigated a link between VWF level and “severity” of COVID-19. There was variability in the descriptions of COVID-19 severity, which included, for example, “critical” or intensive care unit (ICU) admission versus “noncritical” or non-ICU, and acute kidney injury (AKI) versus no AKI. Other comparisons were COVID-19 pneumonia versus non-COVID-19 pneumonia and COVID-19 VTE (venous thromboembolism) versus non-VTE COVID-19. A few reports were also available in regard to levels of VWF:Ag in survivors of COVID-19 versus nonsurvivors (► **Fig. 1D**). In general, the level of VWF:Ag is associated with COVID-19 severity. Thus, the highest levels of VWF:Ag were evident in those with “most severe” disease, as well as in nonsurvivors (► **Fig. 1C, D**).

VWF Activity

As noted earlier, a wide variety of VWF “activities” were reported in COVID-19 studies. The most frequent was for GPIb-binding (GPIbB) activity, using VWF:RCo, VWF:GPIbR,

Table 1 Summary of literature related to VWF and ADAMTS-13 in COVID-19—Part I: (Raised) VWF^a

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Method for VWF	Link to COVID-19 severity
Panigada et al ⁷	Raised VWF:Ag (529 [210–863]) and VWF:RCo (387 [195–550]) in 11/11 ICU patients with COVID-19	11	Mean (min–max)	VWF:Ag and VWF:GPIbR (both Werfen LIA on ACL TOP; model unspecified)	Only in so far as all patients in ICU
Poissy et al ⁸	107 first consecutive patients with confirmed COVID-19 admitted to ICU for pneumonia, PE occurred at unexpected high rate (2× expected)	107	Values not reported	VWF:Ag—method unspecified	VWF:Ag associated with a greater PE risk
Helms et al ⁹	Raised VWF:Ag (455 [350; 521]) and VWF:Act (328 [212; 342]) in 150 COVID-19 patients admitted to ICU for ARDS	150	Median (IQR)	VWF:Ag and VWF:Act—methods unspecified	Only in so far as all patients were in ICU with ARDS
Goshua et al ¹⁰	68 patients with COVID-19, 48 ICU and 20 non-ICU, plus 13 nonhospitalized, asymptomatic controls. VWF:Ag and VWF:Act raised in both COVID-19 groups, but higher in ICU Ag: 565% (199) Act: 390% (390–390)* than non-ICU cohort 278% (133); 260% (145–323) both $p < 0.0001$ (* as reported, but could be an error)	68	VWF:Ag (mean \pm SD); VWF:Act (median, IQR)	VWF:Ag and VWF:Act; Werfen LIA on ACL TOP	Mortality was significantly correlated with VWF:Ag
Ladikou et al ¹¹	24 consecutive severe COVID-19-positive patients (ICU or high acuity ward). VTE rate was 25% and mortality rate was 16.7%. VWF:Ag highly elevated (350 [302–433]) and significantly higher in those who died. Reduced ADAMTS-13 measured in one patient with massive DVT and PE and very high VWF	24	Median (IQR)	VWF:Ag—Stago LIA. VWF:RCo—Stago turbidimetric (data not reported); instrument unspecified; ADAMTS-13—single case—method unspecified	VWF:Ag significantly higher in those who died compared with survivors
Masi et al ¹²	28 consecutive patients with severe ARDS in ICU; 17 COVID-19 and compared with 11 patients with ARDS without COVID-19. VWF:Ag (444 [338–520]) and VWF:Act 286 (173–351) raised in both of normal range, but did not differ between ARDS cohorts	28	Median (IQR)	VWF:Ag and VWF:Act—methods unspecified	Only in so far as all patients had severe ARDS
Sardu et al ¹³	164 hypertensive COVID-19 patients, ABO blood group in 0 ($n = 72$) vs. non-0 ($n = 92$). Raised VWF (239 [115–476]) of normal range. Non-0 had significantly higher VWF 256 [115–476] than 0 group (209 [115–401]) ($p = 0.007$) and higher rates of cardiac injury and death	164	Median (IQR)	VWF method unspecified	VWF higher in non-0 blood group which was an independent predictor of both cardiac injury and deaths in hypertensive patients with COVID-19
Rauch et al ¹⁴	243 adult COVID-19 admission VWF:Ag vs. adverse outcomes (increased oxygen requirements, thrombosis, and death at day 30). VWF levels increased (361 \pm 128) and were highest for patients directly admitted to the ICU	243	Mean \pm SD	VWF:Ag—LIA test LIAPHEN HYPHEN (instrument unspecified)	Higher VWF:Ag in patients admitted to ICU of general wards and in those with higher oxygen requirements (i.e., high-flow oxygen or invasive ventilation) of no oxygen requirement.

Table 1 (Continued)

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Method for VWF	Link to COVID-19 severity
Hoechter et al ¹⁵	22 patients with COVID-19 vs. 14 with another infection (bacterial or viral) pneumonia (control group) with ARDS. VWF:Ag (300 [249, 371]) and VWF:GPIbM (226 [204, 312]) high in 7 tested COVID-19 patients of normal; unavailable in other cohort or other COVID patients	22	Median (IQR)	VWF:Ag (LIA) and VWF: GPIbM (LIA) (both Siemens); instrument unspecified	Thromboembolic complications were also significantly associated with a higher risk of increase in oxygen requirements. Association of VWF:Ag to thrombosis or mortality were nonsignificant
Taus et al ¹⁶	VWF:Ag (280.8 ± 73.1), GPIbR (265.1 ± 71.0) and CB (274.8 ± 61.8) all higher in COVID-19 patients (n = 10) than healthy controls (n = 20)	10	Mean ± SD	VWF:Ag, VWF: GPIbR and VWF:CB (all AcuStar CLIA)	Not reported
Fan et al ¹⁷	12 ICU patients with severe COVID-19 who were on either mechanical ventilation or on high flow oxygen. All had elevated VWF:Ag (320; 259, 371)	12	Median (IQR)	VWF:Ag (Stago LIA on STAR MAX instrument)	Only in so far as all patients had severe COVID-19
Cugno et al ¹⁸	148 patients with COVID-19 of different severity were evaluated upon hospital admission and 30 days later. Patients had high plasma levels of VWF:Ag which paralleled disease severity (mild: [263, 90–435]; moderate [374, 153–652], severe [395, 251–667]). Mild vs. moderate disease (p = 0.001), and between mild and severe patients (p = 0.0001). VWF levels significantly correlated with SC5b-9 levels (p = 0.0001), but not with C5a levels. After 30 days, plasma VWF levels significantly decreased in patients in remission	148	Median (range)	VWF:Ag (HemosIL LIA; instrument unspecified)	Yes, levels of VWF increased with severity of COVID-19
Ward et al ¹⁹	28 patients with COVID-19 admitted to ICU. Markedly increased plasma VWF:Ag (ELISA) in patients with severe COVID-19 365.3 (270.8–568.2), which increased with ICU stay and decreased post-ICU discharge. VWF:Ag levels not different between those with VTE or who died vs. those without VTE and who survived	28	Median (IQR)	VWF:Ag (ELISA; otherwise unspecified)	VWF:Ag levels high in ICU patients with COVID-19, but no difference between VTE/death and non-VTE/survivor groups
Ruberto et al ²⁰	19 COVID-19 patients vs. 10 healthy volunteers. VWF:Ag (331.4 ± 104.5) and VWF:RCO (321.7 ± 149.4) elevated in COVID-19 patients	19	Mean ± SD?	VWF:Ag and VWF:RCO (methods unspecified)	Not evaluated

(Continued)

Table 1 (Continued)

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Method for VWF	Link to COVID-19 severity
Heinz et al ²¹	27 COVID-19 patients. VWF:Ag (554 [431–600]) elevated in all COVID-19 patients	27	Median (IQR)	VWF:Ag measured on ACL Top 700 CTS (presumed LIA)	Not evaluated
Philippe et al ²²	208 COVID-19 patients (23 “mild” outpatients, 189 hospitalized). Most endothelial biomarkers found increased in the 89 critical patients transferred to ICU. However, only VWF:Ag scaled according to clinical severity, with levels significantly higher in critical patients (507, 428–596) compared with noncritical patients (288, 230–350, $p < 0.0001$) or COVID-19 outpatients (144, 133–198, $p = 0.007$). Similar for VWF:RCo (399 [333–537] vs. 231 [174–276] vs. 122 [95–161]). Moreover, VWF HMWMs were significantly higher in critical patients (median ratio: 1.18, IQR: 0.86–1.09) compared with noncritical patients (0.96, 1.04–1.39, $p < 0.001$). Among all endothelial biomarkers measured, ROC curve analysis identified a VWF:Ag cut-off of 423% as the best predictor for in-hospital mortality	208	Median (IQR)	VWF:Ag (LIA) and VWF:RCo (turbidimetric) Stago methods on STAR Max analyzer; VWF multimers on Hydrasys 2 Scan instrument	“VWF:Ag is a relevant predictive factor for in-hospital mortality in COVID-19 patients. More than a biomarker, we hypothesize that VWF, including excess of HMWMI forms, drives microthrombosis in COVID-19”
Vassiliou et al ²³	38 critically ill COVID-19 ICU patients; 28 survivors and 10 nonsurvivors; VWF:Ag (higher in non-survivors ($p = 0.008$))	38	VWF:Ag reported in ng/mL	VWF:Ag (ELISA; R&D systems)	VWF:Ag higher in nonsurvivors than in survivors
Bauer et al ²⁴	17 COVID-19 patients (10 non-ICU, 7 ICU) vs. 41 non-COVID-19 patients (31 non-ICU, 10 ICU). Higher VWF:Ag in ICU COVID-19 vs. non-ICU COVID-19	17	Median (IQR)	VWF:Ag (LIA, Stago, STAR MAX) VWF:RCo agglutination (Siemens Behring Coagulation System XP)	Higher VWF:Ag in ICU COVID-19 vs. non-ICU COVID-19

Abbreviations: ARDS, acute respiratory distress syndrome; cf, compared with; CLIA, chemiluminescence immunoassay (AcuStar); ELISA, enzyme-linked immunosorbent assay; HMWMI, high-molecular-weight multimers; IH, in house; IQR, interquartile range; LIA, latex immunoassay (agglutination); max, maximum; min, minimum; SD, standard deviation; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:CB, VWF collagen binding; VWF:GP1bM, VWF glycoprotein 1b (mutant) binding assay; VWF:GPIbR, VWF glycoprotein 1b (recombinant) binding assay; VWF:RCo, VWF ristocetin cofactor (glycoprotein 1b binding assay using platelets and ristocetin).

^aData exclude single case studies, and listed in order of PubMed listing. Note that wide variety of methods (not always documented) may be used to assess VWF. This will have an influence on findings, but this is not always understood by authors who report on findings. Values reported in publications in U/mL have been converted to U/dL for clearer comparisons.

Table 2 Summary of literature related to VWF and ADAMTS-13 in COVID-19—Part II: (raised) VWF and (lowered) ADAMTS-13^a

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Methods for VWF and ADAMTS-13	Link to COVID-19 severity
Huisman et al ²⁸	Lowered ADAMTS-13 and raised VWF:Ag (408 [90] and VWF:GPIIbR 374 [105] levels (and raised VWF/ADAMTS-13 ratio; mean 8.5 [6.7]) in 12 patients with a clinical suspicion of microangiopathy in severe COVID-19 in ICU (all ventilator use)	12	Mean ± SD	VWF:Ag, VWF: GPIIbR and ADAMTS-13 all by AcuStar CLIA	Only in so far as all patients were in ICU/ventilator use
Bazzan et al ²⁹	88 consecutive COVID-19 admitted patients; ADAMTS-13 reduced (nonsurvivors: 32, 16 vs. survivors: 51, 18) in 88/88 cf healthy controls; no ADAMTS-13 antibodies detected; raised VWF (non-survivors 396, 113 vs. 296, 133 survivors) in COVID-19 cohort also; VWF/ADAMTS-13 ratio not reported, but would be raised	88	Mean ± SD	VWF:Ag and ADAMTS-13 by AcuStar CLIA method	Overall, cohort mortality rate of 10.2% (9/88). Patients who died had significant lower levels of ADAMTS-13 and higher levels of VWF when compared with patients with nonfatal outcome
Morici et al ³⁰	VWF (Ag, GPIbR, CB) increased in 6/6 and ADAMTS-13 reduced in 5/6 patients with COVID-19 in ICU. 1/6 displayed mild level of antibodies to ADAMTS-13; VWF/ADAMTS-13 ratio not reported, but would be raised	6	Reported individual values	VWF:Ag, VWF: GPIIbR, VWF:CB; ADAMTS-13—all by AcuStar CLIA method	Only in so far as all patients had severe COVID-19
Blasi et al ³¹	23 patients with COVID-19 who were on prophylactic or intensified anticoagulant therapy (12 ICU; 11 general wards). COVID-19 patients had high VWF:Ag levels (306 [200–421]) and low ADAMTS-13 activity (47.3 [25.8–66.1]) (2 patients <10%). VWF/ADAMTS-13 ratio not reported, but would be raised	23	Median (IQR)	VWF:Ag (IH ELISA); ADAMTS-13 activity (Pep-taNova FRETs assay)	VWF:Ag higher in patients with severe COVID-19 (ICU) cf other wards. ADAMTS-13 reduced in both cohorts, but not significantly different between cohorts
Tiscia et al ³²	77 patients admitted with COVID-19. Raised VWF:Ag (231.2 [415.3–205.7]), generally raised VWF:RCo (150.0 [334.3–116.9]), and reduced VWF:RCo/Ag ratio 0.65 (0.87–0.6) and ADAMTS-13/VWF:RCo 0.40 (0.50–0.23). ADAMTS-13 generally in low end of NRR (70 [80–60]). VWF:Ag inversely associated with ADAMTS-13	77	Median (IQR)	VWF:Ag and VWF: RCo (methods unspecified); ADAMTS-13 (Technozym ELISA)	Reduced probability of survival when ADAMTS-13 <70 (p = 0.025). No association of survival with VWF:RCo
Fraser et al ³³	10 COVID-19 patients compared with healthy control subjects, COVID-19-positive patients had raised plasma VWF:Ag; no reduction observed in ADAMTS-13	10	VWF:Ag reported as ng/mL; ADAMTS-13 levels not reported	VWF:Ag (Thermo Fisher ELISA); ADAMTS-13 (Abcam ELISA)	Not evaluated
Sweeney et al ³⁴	181 hospitalized COVID-19 patients randomly selected with equal distribution of survivors and nonsurvivors. Patients who died had significantly lower ADAMTS-13 activity (48.8 [36.2, 65.1] vs. 63.6 [47.2, 78.9]; p ≤ 0.001), significantly higher VWF levels (441.0 [307.6, 598.0] vs. 362.0 [261.0, 540.0]; p = 0.05), compared with patients discharged alive. Only 30% of patients with an initial	181	Median (IQR)	VWF:Ag (LIA) and VWF:RCo (agglutination) on STAR; VWF:CB Hyphen ELISA; ADAMTS-13 activity (FRETs,	Nonsurvivors had significantly lower ADAMTS-13 activity levels and higher VWF (Ag, RCo). ADAMTS-13 activity inversely correlated with VWF (RCo, CB).

(Continued)

Table 2 (Continued)

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Methods for VWF and ADAMTS-13	Link to COVID-19 severity
	ADAMTS-13 activity <43% survived vs. 60% with ADAMTS-13 \geq 43% who survived. ADAMTS-13 antibodies not detected in those with ADAMTS-13 <30%. VWF/ADAMTS-13 ratio not reported, but would be raised. Many COVID-19 patients had an increased density of HMW compared with normal pooled plasma			Immucor) and Antigen (Technozym) and antibodies (Technozym). Multi-lumers IH western blot method	Patients with thrombosis exhibited significantly higher VWF activity. Although the number of patients with documented thrombosis (both in vivo and ex vivo) was not significantly different based on ADAMTS-13 levels, ex vivo clots, such as clots in the hemodialysis lines, were mainly observed in patients with ADAMTS-13 levels lower than the normal range <70% (10 patients [7.8%] vs. 1 (1.9%); $p = 0.181$). Only 30% (10/33) of patients with an ADAMTS-13 activity <43% within 72 hours of admission survived compared with 60% (41/69) 336 with ADAMTS-13 $>$ 43% who survived. The number of patients who required ventilation with an initial ADAMTS-13 <43% was more than twice that of patients with initial ADAMTS-13 $>$ 43% (12/33 (36%) vs. 11/69 (16%); $p = 0.04$)
Hardy et al ³⁵	21 ICU admitted patients with COVID-19. VWF:Ag (438 [357–534]) and VWF:GPIIbR (294 [228–452]) elevated and ADAMTS-13 activity (61 [40–65]) reduced. VWF/ADAMTS-13 ratio not reported, but would be raised	21	Median (IQR)	VWF:Ag (Stago LIA on STAR MAX); VWF:GPIIbR (AcuStar CLIA); ADAMTS-13 activity (Technozym)	Not evaluated
Mancini et al ³⁶	VWF:Ag and VWF:RCo and ADAMTS-13 in 50 patients stratified according to admission to 3 different intensity of care units: low (requiring high-flow nasal cannula oxygenation, $n = 14$), intermediate (requiring continuous positive airway pressure devices, $n = 17$), and high (requiring mechanical ventilation, $n = 19$). Median VWF:Ag, VWF:RCo, levels markedly elevated in COVID-19 patients and	50	Median (IQR)	VWF:Ag and VWF:GPIIbR (Hemosil reagents on ACL TOP 700); ADAMTS-13 (IH FRET); multimers	Significant alteration of the VWF-ADAMTS-13 axis in COVID-19 patients, with an elevated VWF:Ag to ADAMTS-13 activity ratio of 6.07 (3.62–8.59) was

Table 2 (Continued)

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Methods for VWF and ADAMTS-13	Link to COVID-19 severity
Henry et al ³⁷	increased with intensity of care, with median VWF:Ag being 268, 386, and 476 IU/dL; VWF:RCo 216, 334, and 388 IU/dL; in patients at low, intermediate, and high intensity of care, respectively. Conversely, high-to-low molecular-weight VWF multimers ratios progressively decreased with increasing intensity of care, as well as median ADAMTS-13 activity levels, which ranged from 82 IU/dL for patients at low intensity of care to 62 and 55 IU/dL for those at intermediate and high intensity of care	52	Median (IQR)	VWF:Ag (Technozym ELISA); ADAMTS-13 activity (IH FRETs)	strongly associated with disease severity (medians: 3.42, 6.77, 8.33 in low, medium, high, respectively). Such an imbalance enhances the hypercoagulable state of COVID-19 patients and their risk of microthrombosis
Arulkumar et al ³⁸	52 adult COVID-19 patients stratified by presence of acute kidney injury. 23.1% of cohort had a relative deficiency in ADAMTS-13 activity, while 80.8% had elevated VWF:Ag. ADAMTS-13 activity/VWF:Ag ratio was significantly lower in patients with severe AKI (0.21 [0.18–0.33] vs. 0.36 [0.28–0.48]) $p = 0.002$ and those who developed severe COVID-19 (0.24 [0.20–0.36] vs. 0.36 [0.28–0.48]; $p = 0.020$)	7	Median (IQR)	VWF:Ag and VWF:GPIbM (Siemens on CS2500); ADAMTS-13 (IH FRETs)	Potentially; PEx treatment reduced VWF and VWF/ADAMTS-13 ratio with clinical improvement in COVID-19 patients
Delrue et al ³⁹	133 patients with COVID-19; 38 with VTE, 95 without VTE; 68 critically ill ICU and 65 noncritically ill general ward patients. VTE occurred in 38 patients including isolated DVT in 24 (63%); 13 distal and 1 proximal), isolated PE in 9 (24%) and both PE/DVT in 5 (13%). Death occurred in 23 patients (17%). VWF:Ag elevated in all patients in both cohorts, but higher in VTE cohort (522 [411–672] cf 473 [311–589]) ($p = 0.05$). ADAMTS-13 reduced in proportion of VTE cohort, and levels statistically less in VTE cohort 59.0 [38.8–70.5] than non-VTE cohort 68.5 [52.0–87.5] ($p = 0.005$). ADAMTS-13 activity was also significantly lower in nonsurvivors vs. survivors ($p < 0.0001$). VWF/ADAMTS-13 ratio not reported, but would be raised	133	Median (IQR)	VWF:Ag (Stago ELISA); ADAMTS-13 (IH FRETs)	VWF:Ag higher in VTE cohort and ADAMTS-13 (FRETs) statistically less in VTE cohort than in non-VTE cohort. ADAMTS-13 activity was also significantly lower in nonsurvivors vs. survivors ($p < 0.0001$)
Fernández-Pérez et al ⁴⁰	142 hospitalized COVID-19 patients. VWF:Ag/ADAMTS-13 ratio seemed to account for severity, given association with clinical scores, hypercoagulable state, acute respiratory distress syndrome, ICU admission, and mortality. Patients with lower ADAMTS-13 activity (<63%) had lower survival	142	values plotted but not numerically reported	VWF:Ag and ADAMTS-13 activity—methods not specified	VWF/ADAMTS-13 axis imbalance may have an impact on patient's prognosis
Rodríguez Rodríguez et al ⁴¹	100 consecutive hospitalized COVID-19 patients, 50 nonsevere disease vs. 50 severe disease; 81 survivors, 19 nonsurvivors. Severe cases and nonsurvivors had significantly lower ADAMTS-13 activity (53.2 [38.8–65.3] and 42.4 [33.8–57.3], respectively) and higher	100	Median (IQR)	VWF:Ag and ADAMTS-13 both AcuStar CLIA	Significantly lower ADAMTS-13 activity and higher VWF in severe cases and nonsurvivors than

(Continued)

Table 2 (Continued)

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Methods for VWF and ADAMTS-13	Link to COVID-19 severity
	VWF (355 [267–400] and 395 [294–400], respectively) than non-severe (ADAMTS-13: 69 [54.2–84.9]; VWF:Ag–261.4 [213–326] and survivors (ADAMTS-13: 62.8 [52.3–80.1]; VWF:Ag–270 [218–353]), respectively. ADAMTS-13 activity was negatively correlated with VWF:Ag. 15 out of 19 nonsurvivors had ADAMTS-13 activity lower than 61%. VWF/ADAMTS-13 ratio not reported, but would be raised				nonsevere and survivors, respectively
De Jongh et al ⁴²	16 ICU COVID-19 patients (5 nonsurvivors vs. 11 survivors). Non-significantly higher VWF:Ag in nonsurvivors (260.4, 12.7 vs. 235.0 38.3), but significantly higher “active” VWF (217.6 36.8 vs. 173.7 83.0; $p = 0.05$) and significantly lower ADAMTS-13 ($p = 0.01$) in nonsurvivors. VWF/ADAMTS-13 ratio not reported, but would be raised	16	Mean \pm SD	VWF:Ag and “active” VWF (IH ELISA); ADAMTS-13 (Biomedica Diagnostics, FRETs) ng/mL	Significantly higher “active” VWF and significantly lower ADAMTS-13 in nonsurvivors of survivors
De Cristofaro et al ⁴³	VWF:Ag and VWF:GPIIB and ADAMTS-13 measured in 10 COVID-19 pneumonia patients vs. 10 non-COVID-19 pneumonia patients. VWF:Ag and VWF:RC0 significantly elevated in COVID-19 pneumonia patients (324.1 [271.8–416] vs. 153 [135–173] IU/dL, $p < 0.0001$ and (341.5 [267–413.8] vs. 133 [119–155] IU/dL, $p < 0.001$, respectively) vs. non-COVID-19 pneumonia patients; ADAMTS-13 normal in both groups. ADAMTS-13/VWF significantly lower in COVID-19 pneumonia patients (0.218 [0.15–0.246] vs. 0.42 [0.39–0.65], $p < 0.0001$)	10	Median (IQR)	VWF:Ag and VWF: GPIIB (both CLIA AcuStar) and ADAMTS-13 (FRETs; ACTI-FLUOR; Sekisui Diagnostics)	VWF significantly elevated and ADAMTS-13/VWF significantly lower in COVID-19 pneumonia patients vs. non-COVID-19 pneumonia patients
von Meijenfheldt et al ⁴⁴	102 patients with COVID-19 receiving various levels of respiratory support admitted to general wards, intermediate units, or ICU. VWF levels increased, and ADAMTS-13 levels decreased, with increasing respiratory support. Low levels of ADAMTS-13, and high levels of VWF were associated with short-term mortality	102	Median (IQR)	VWF:Ag (IH ELISA); ADAMTS-13 (PeptaNova FRETs)	VWF levels increased, and ADAMTS-13 levels decreased, with increasing respiratory support. Low levels of ADAMTS-13 and high levels of VWF were associated with short-term mortality
Falter et al ⁴⁵	22 COVID-19 patients comprehensively tested for the presence of TMA: Elevated levels of VWF activity (329, 195 to >390) and antigen (232, 219–498) levels. Elevated VWF antigen/ADAMTS-13 activity ratio in 21/21 (100%) patients tested (3.4, 2.6–7.7; range: 2.1–33.4). ADAMTS-13 was mostly in the normal range and only 4/22 tested showed reduced ADAMTS-13 activity values (<50%) with a minimum ADAMTS-13 activity of 17.8%	22	Median (IQR)	VWF:Ag and VWF: Act methods unspecified; ADAMTS-13 activity (IH FRETs)	Not reported
Pascreau et al ⁴⁶	70 patients with COVID-19 separated into home discharge ($n = 4$), admission to ICU ($n = 22$), or non-ICU ward ($n = 44$) vs. controls ($n = 21$). VWF:Ag and VWF:Act increased and ADAMTS-13 decreased with increasing COVID-19 severity; VWF levels higher and ADAMTS-13 levels lower in nonsurvivors than in survivors	70	Median (IQR); ADAMTS-13 reported in ng/mL	VWF:Ag and VWF: Act (Hemosil, presumably LIA, unspecified instrument). ADAMTS-13	VWF:Ag and VWF:Act increased and ADAMTS-13 decreased with increasing COVID-19 severity; VWF levels higher and ADAMTS-13

Table 2 (Continued)

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Methods for VWF and ADAMTS-13	Link to COVID-19 severity
Doevelaar et al ⁴⁷	75 COVID-19 varied severity vs. 30 healthy controls. VWF:Ag cases 403 ± 218 vs. 0.99 ± 0.31 (<i>p</i> < 0.001). ADAMTS-13 cases 67.8 ± 22.4 vs. 73.9 ± 15.5 (<i>p</i> = 0.176). ADAMTS-13/VWF 0.244 ± 20.5 vs. 0.820 ± 0.307 (<i>p</i> < 0.001). Large multimers in COVID-19 patients were significantly lower than in healthy pool samples (68.69% ± 16.16% vs. 112.04% ± 13.31%; <i>p</i> < 0.0001)	75	Mean ± SD	antigen, method unspecified VWF:Ag (IH ELISA), VWF multimers (IH); ADAMTS-13 (TechnoZyme ELISA)	13 levels lower in nonsurvivors than in survivors The ratio of ADAMTS-13/VWF:Ag decreased continuously with the degree of COVID-19 severity (ANOVA, <i>p</i> = 0.026). ADAMTS-13 and ADAMTS-13/VWF:Ag ratios were significantly lower in subjects who did not survive COVID-19 (72.6 ± 20.4 vs. 45.2 ± 18.0; <i>p</i> < 0.001 for ADAMTS-13 and 0.268 ± 0.214 vs. 0.130 ± 0.103; <i>p</i> = 0.001 for ADAMTS-13/VWF ratio). VWF:Ag did not significantly differ between survivors and those who died (<i>p</i> = 0.181). "COVID-19 is associated with a substantial increase in VWF levels, which can exceed the ADAMTS-13-processing capacity resulting in the formation of large VWF multimers indistinguishable from thrombotic thrombocytopenic purpura.")

Abbreviations: ARDS, acute respiratory distress syndrome; cf, compared with; CLIA, chemiluminescence immunoassay (AcuStar); ELISA, enzyme-linked immunosorbent assay; IH, in house; IQR, interquartile range; LIA, latex immunoassay (agglutination); min, minimum; max, maximum; SD, standard deviation; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:CB, VWF collagen binding; VWF:GPIIb, VWF glycoprotein Ib (mutant) binding assay; VWF:GPIbR, VWF glycoprotein Ib (recombinant) binding assay; VWF:RCo, VWF ristocetin cofactor (glycoprotein Ib binding assay using platelets and ristocetin).
^aData exclude single case studies, and listed in order of PubMed listing. Note that wide variety of methods (not always documented) may be used to assess VWF and ADAMTS-13. This will have an influence on findings, but this is not always understood by authors who report on findings. Values reported in publications in U/ml have been converted to U/dL for clearer comparisons.

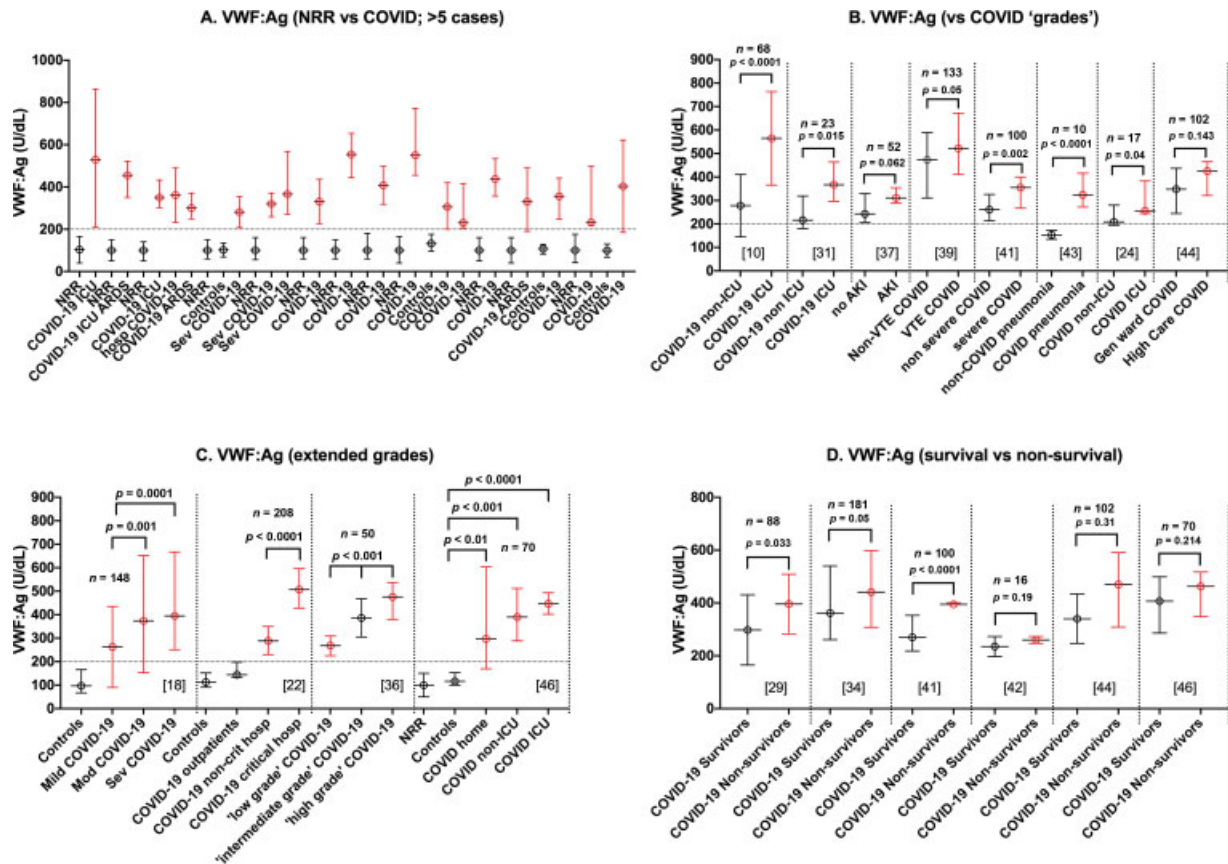


Fig. 1 Values of von Willebrand factor antigen (VWF:Ag) reported in the literature for cases of coronavirus disease (COVID)-19, where more than five cases were reported. (A) VWF:Ag (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 (shown in red) versus normal reference ranges (NRRs) or control groups (shown in black). In general, NRRs were around 50–200 U/dL, whereas VWF:Ag in COVID-19 cases were invariably higher, with some cases reporting >600 U/dL. (B) VWF:Ag (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 of differing “severity.” (C) VWF:Ag (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 of increasing “severity.” (D) VWF:Ag (left Y-axis) in U/dL (= % of normal) for survivor versus nonsurvivor cohorts of COVID-19. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; VTE, venous thromboembolism. Ranges are either median/interquartile range (IQR) or mean \pm standard deviation (SD)—as noted in **►Tables 1** and **2**. References are given in square brackets. Numbers of cases and reported *p*-values are also given in some figures.

or VWF:GPIbB assays (**►Fig. 2**). **►Figure 2A** summarizes reports identifying the level of VWF:GPIbB in cases of COVID-19 versus NRRs or controls, where more than five cases of COVID-19 were reported. Like VWF:Ag, although the expected NRR for VWF:GPIbB assays would approximate 50 to 200 U/dL (or % of normal), the literature on COVID-19 again matches the general VWF literature and the reported NRR varied widely among the studies (as thus dependent on test, method, and study population) (**►Tables 1** and **2**). Nevertheless, in general, the upper limit of normal for VWF:GPIbB assays was again (like VWF:Ag) below 200 U/dL (or %). In all studies, again comprising various cohorts of COVID-19 patients, median values for VWF:GPIbB assays in infected patients were always well above 200 U/dL, and, indeed, so too were most of the reported lower limits of IQR or SD values (**►Fig. 2A**).

►Figure 2(B, C) shows additional data on VWF:GPIbB assays in COVID-19, where reports investigated a link between level of VWF and severity of COVID-19. Again, given that the studies comprised a subset of the reported VWF:Ag studies, there was similar variability in the descriptions of COVID-19 severity. In general, the level of VWF:GPIbB activi-

ty was associated with severity of COVID-19, and was similar to VWF:Ag, with highest levels evident in those with “most severe” disease, as well as in nonsurvivors. Nevertheless, it should be noted that absolute levels in general were not reported to be as numerically high as those for VWF:Ag. Thus, although VWF:Ag levels were sometimes reported as above 600 U/dL, those for VWF:GPIbB were not, reaching maximums closer to 400 U/dL. It is unclear whether this reflects a true differential in VWF:GPIbB versus VWF:Ag in COVID-19, or is simply an artifact of the assays used, which are more often used to identify or exclude VWD (and thus the linear portion of the assay range tends to be <100 U/dL).⁴⁸

Levels of VWF collagen binding (VWF:CB) were reported only in three studies (**►Fig. 2D**), with mixed findings, most likely dependent on both the COVID-19 cohort and the reported VWF:CB method. For example, two studies reported on VWF:CB by chemiluminescent immunoassay (CLIA) method on the ACL AcuStar instrument, but with small numbers of COVID-19 patients ($n = 6$, $n = 10$). Nevertheless, this method is highly discriminatory for HMW forms of VWF.⁴⁹ In contrast, one large study ($n = 181$) utilized a commercial ELISA (enzyme-linked immunosorbent assay).

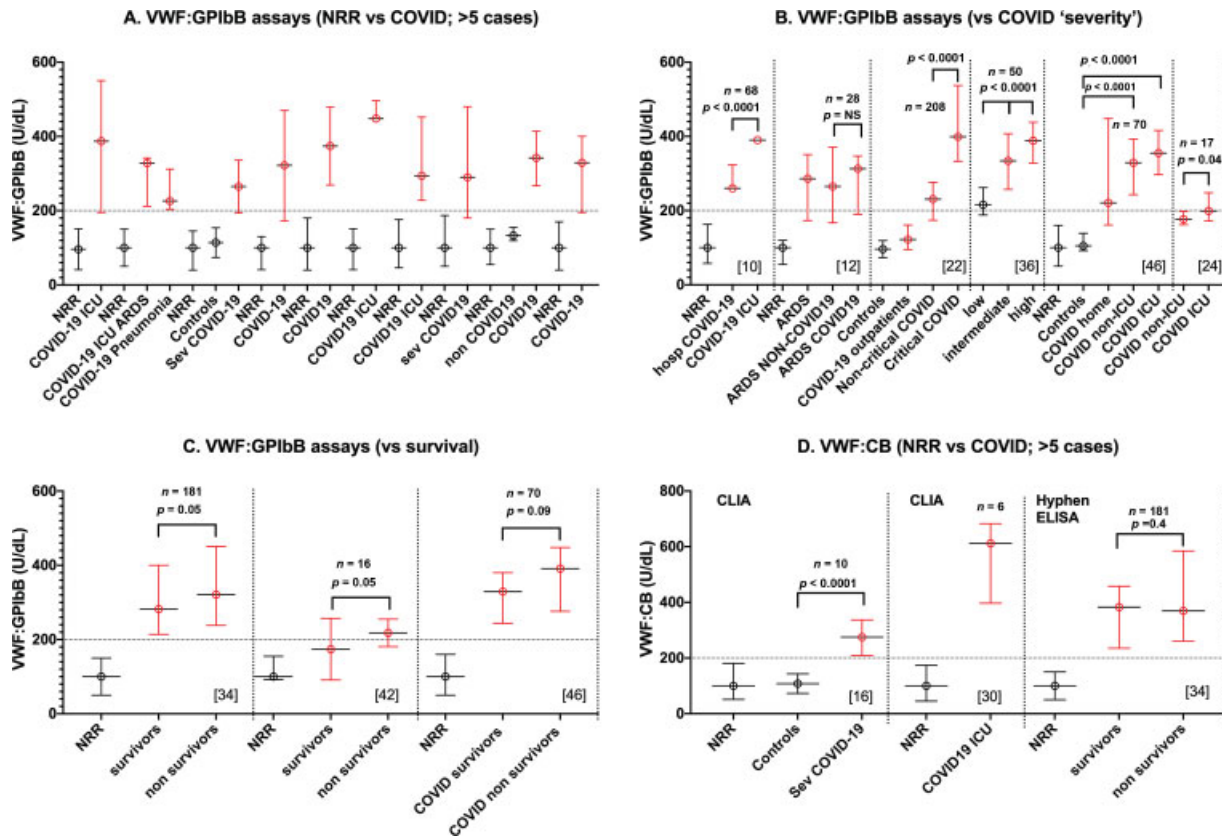


Fig. 2 Values of von Willebrand factor glycoprotein Ib binding (VWF:GPIbB) or collagen binding (VWF:CB) activity reported in the literature for cases of coronavirus disease (COVID)-19, where more than five cases reported. VWF:GPIbB activity may include ristocetin cofactor [VWF:RCo] or more modern versions including VWF:GPIbR [recombinant] and VWF:GPIbM [mutant]. (A) VWF:GPIbB (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 (shown in red) versus normal reference ranges (NRRs) or control groups (shown in black). In general, NRRs were around 50–200 U/dL, whereas COVID-19 cases were invariably higher, with some cases reporting >400 U/dL. (B) VWF:GPIbB (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 of differing or increasing “severity.” (C) VWF:GPIbB (left Y-axis) in U/dL (= % of normal) for survivor versus nonsurvivor cohorts of COVID-19. (D) VWF:CB (left Y-axis) in U/dL (= % of normal) for the three studies reporting levels in COVID-19. ARDS, acute respiratory distress syndrome; ICU, intensive care unit. Ranges are either median/interquartile range (IQR) or mean \pm standard deviation (SD)—as noted in ► Tables 1 and 2. References given in square brackets. Numbers of cases and reported *p*-values also given in some figures.

The Westmead laboratory has previously identified that commercial VWF:CB assays may vary significantly in regard to relative discrimination of HMW VWF.⁵⁰

A small number of studies also reported on other VWF test parameters, such as VWF propeptide (VWFpp)¹⁹ and “active” VWF using a novel assay.⁴² In general, these could also be associated with COVID-19 severity. Ward et al¹⁹ reported plasma VWFpp levels were markedly elevated in severe COVID-19 (median [IQR] 325 [267–524] U/dL). Interestingly, however, they also reported that the VWFpp/VWF:Ag ratio was reduced in severe COVID-19, perhaps demonstrating that decreased VWF clearance contributes to elevated plasma VWF:Ag levels in severe COVID-19. They also reported that plasma VWFpp levels also correlated with clinical severity indices such as the Sequential Organ Failure Assessment (SOFA) score, Sepsis-Induced Coagulopathy (SIC) score, and the ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio). Collectively, the authors concluded that these findings supported the hypothesis that sustained fulminant endothelial cell activation occurs in severe

COVID-19, and that VWFpp may have a role as a biomarker in this setting. De Jongh et al⁴² reported higher “active” VWF (217.6 ± 36.8 vs. 173.7 ± 83.0 ; $p = 0.05$) in nonsurvivors than in survivors, using a novel method to identify “active” VWF.

VWF Multimers

VWF multimers were reported in few studies. Of interest, one system called Hydrasys permits quantification of multimers using desitometry.^{51–53} This system also permits numerical separation of multimers into low-molecular-weight (LMW), intermediate-molecular-weight VWF, and HMW VWF.^{51–53} Two studies reported results using this method in COVID-19 (► Fig. 3).^{22,36} Interestingly, these reports appear to be at odds with each other. Philippe et al²² reported a comparative increase in HMW VWF and a comparative decrease in LMW VWF with critical COVID-19 (vs. “noncritical”) COVID-19, as one might expect in secondary thrombotic microangiopathies expressing reduced ADAMTS-13. Conversely, and counterintuitively, Mancini et al³⁶ reported a decreasing level of HMW VWF, as well as a reduction in HMW

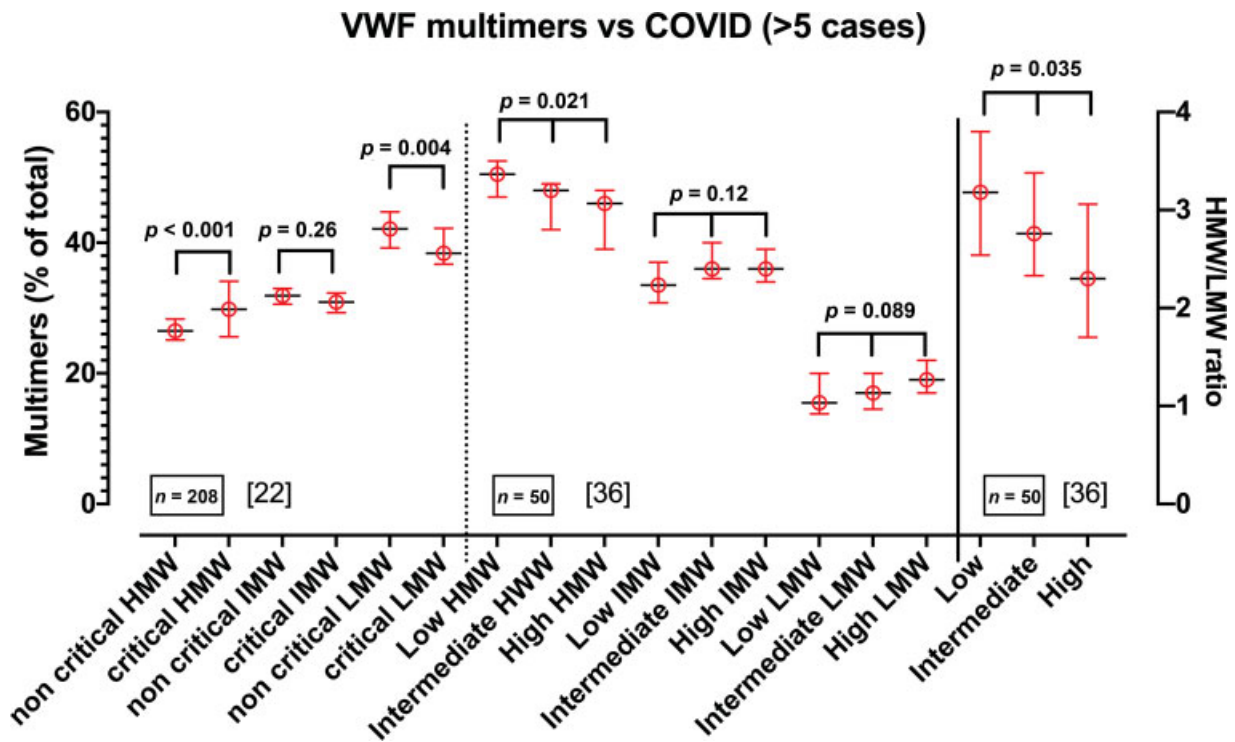


Fig. 3 Values of various fractions of von Willebrand factor (VWF) multimers reported in the literature for cases of coronavirus disease (COVID)-19. VWF multimer fractions were separated into high-molecular-weight (HMW), intermediate-molecular-weight (IMW), and low-molecular-weight (LMW) forms. Left Y-axis reporting as percent of total fraction (=100%). X-axis indicates study population for COVID-19, including grade of severity. Right Y-axis identifies HMW/LMW ratio as reported in one study. Unfortunately, neither study reported the expected values for normal individuals. References given in square brackets. Numbers of cases and reported *p*-values also given.

VWF/LMW VWF ratio, with increasing severity of COVID-19. They suggested that these findings might be explained by an early increase in VWF proteolysis by ADAMTS-13, which must overcome the massive release of VWF multimers by activated endothelium as a consequence of local inflammation. Thus, differences between studies may relate to the time of testing in relation to the COVID-19 time-course. On the other hand, it can be noted that the numerical values reported seem to also differ between the studies. Thus, Philippe et al²² reported a relatively higher proportion of LMW forms (~40% of the total) of VWF than HMW VWF (~25–30% of the total) in test samples, whereas Mancini et al³⁶ reported the reverse (~20% of the total represented by LMW VWF vs. approximately 40 to 45% of the total represented by HMW VWF). This difference, given both groups reported to use the same method, needs clarification. Using this system and normal individuals, approximately 20% of the total is represented by LMW VWF while approximately 40 to 45% of the total is represented by HMW VWF,⁵² which more closely aligns to separations reported by Mancini et al³⁶ for COVID-19 cases.

VWF Activity/Ag Ratio

A minority of studies also reported VWF activity/Ag ratios (–Fig. 4). These were all based on VWF:GPIbB assays (1× VWF:RCo, and 2× VWF:GPIbR) or a monoclonal antibody-based VWF assay (VWF:Ab).^{22,36,43,46} One study found increased VWF:GPIbR/Ag ratio in COVID-19-associated pneumonia versus non-COVID-19-associated pneumonia, albeit

in small cohort numbers ($n = 10$ for each).⁴³ In contrast, the other three studies did not find any statistical association of VWF activity/Ag ratios with COVID-19 severity. We could not find any study reporting on VWF:CB/Ag ratios.

ADAMTS-13 Activity in COVID-19

►Figure 5A summarizes reports identifying the level of ADAMTS-13 activity in cases of COVID-19 versus NRRs or controls, where more than five cases of COVID-19 were reported. Of interest, the expected NRR for ADAMTS-13 activity would approximate 50 to 150 U/dL (or % of normal); however, the literature on COVID-19 (analogous to the situation with VWF) matches the general literature on ADAMTS-13 and the reported NRR varies widely based on the report (and thus the ADAMTS-13 method used; ►Tables 2 and 3). Nevertheless, the lower limit of normal was generally close to 50 U/dL (or %). In all studies, comprising various cohorts of COVID-19 patients, median values among infected patients were generally reduced compared with the expected median of the NRR (being ~100 U/dL). Moreover, the reported lower limits of IQR or SD values were almost always below 50 U/dL.

►Figure 5(B, C) shows additional data on ADAMTS-13 activity in COVID-19, where reports investigated a link between ADAMTS-13 level and severity of COVID-19. Again, there was variability in the descriptions of COVID-19 severity in these reports, similar to the reports describing VWF parameters. The vast majority of reports indicated an

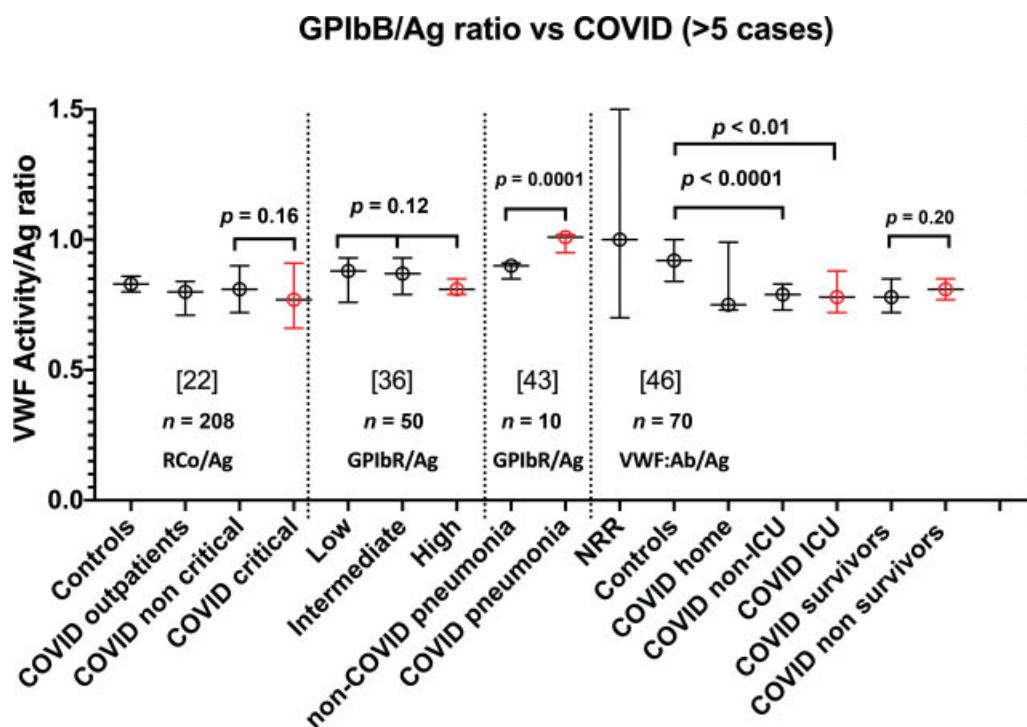


Fig. 4 Values of von Willebrand factor (VWF) activity/Ag ratios (Y-axis) reported in the literature for cases of coronavirus disease (COVID)-19, where more than five cases reported. X-axis indicates study population for COVID-19, including grade of severity. References given in square brackets. Numbers of cases and reported p -values are also given. NRR, normal reference range; ICU, intensive care unit.

association with COVID-19 severity, such that reduced levels of ADAMTS-13 were found in the “sickest” COVID-19 patients (► Fig. 5B) as well nonsurvivors (► Fig. 5C).

VWF/ADAMTS-13 Ratio in COVID-19

It was interesting that many studies reporting both VWF and ADAMTS-13 values also remarked on the finding of higher relative VWF/ADAMTS-13 in COVID-19 patients. However, very few studies actually provided numerical values (► Fig. 6). Invariably when reported, elevated VWF/ADAMTS-13 (or reduced ADAMTS-13/VWF) ratios were found in patients with COVID-19, and these values also associated with disease severity, being the highest in those with worse illness or in nonsurvivors.

Discussion

We report on the VWF/ADAMTS-13 axis in COVID-19, characterized by a general increase in VWF level and activity, as well as by a general decrease in ADAMTS-13 activity. Values for various test parameters were also sometimes able to be associated with disease severity, including survival. Nevertheless, the literature becomes complicated because of different and sometimes diffuse definitions of “disease severity.” The literature is also complicated by the use of many different assay methods, potentially leading to differing conclusions.

In general, VWF:Ag methods are “similar” in that they use antibodies against VWF to detect the level of VWF protein.

However, there are a variety of methodologies in use, including ELISA, latex immunoassay (LIA), and CLIA. Furthermore, ELISAs may be performed as in-house methods or by various commercial methods; these would use different antibodies and assay calibrators, and thus lead to somewhat differing values. LIA assays also would be provided by different manufacturers using different antibodies, assay calibrators, and instruments that will also lead to somewhat differing values. This expected variation can be evidenced, by the differing NRRs reported in the literature, both for COVID-19 (► Fig. 1A) and for VWD testing,⁴⁸ although these NRRs could also be potentially reflective of differing normal populations.

VWF activity methods will differ even more than VWF:Ag assays.⁴⁸ The main VWF activity generally investigated is GPIIb. In turn, this activity may be assessed by VWF:RCo assays (using platelets and ristocetin), VWF:GPIb assays (using inert particles such as latex or magnetic beads bound to recombinant GPIb, together with ristocetin), and finally VWF:GPIbM assays (using inert particles such as latex bound to recombinant-mutated GPIb, without ristocetin).⁴⁸ Thus, the NRRs for VWF:GPIb assays would vary even more between different studies than would VWF:Ag, and accordingly so to many findings in COVID-19 patients.

ADAMTS-13 activity is also measured in many different ways, and this will also influence NRRs (► Fig. 5A), as well as values reported in COVID-19 patients. Most studies reported using FRET-based activity assays, but these were either in-house assays or from a variety of different commercial manufacturers. Some studies reported on levels of ADAMTS-13 detected as “antigen” (i.e., not activity).

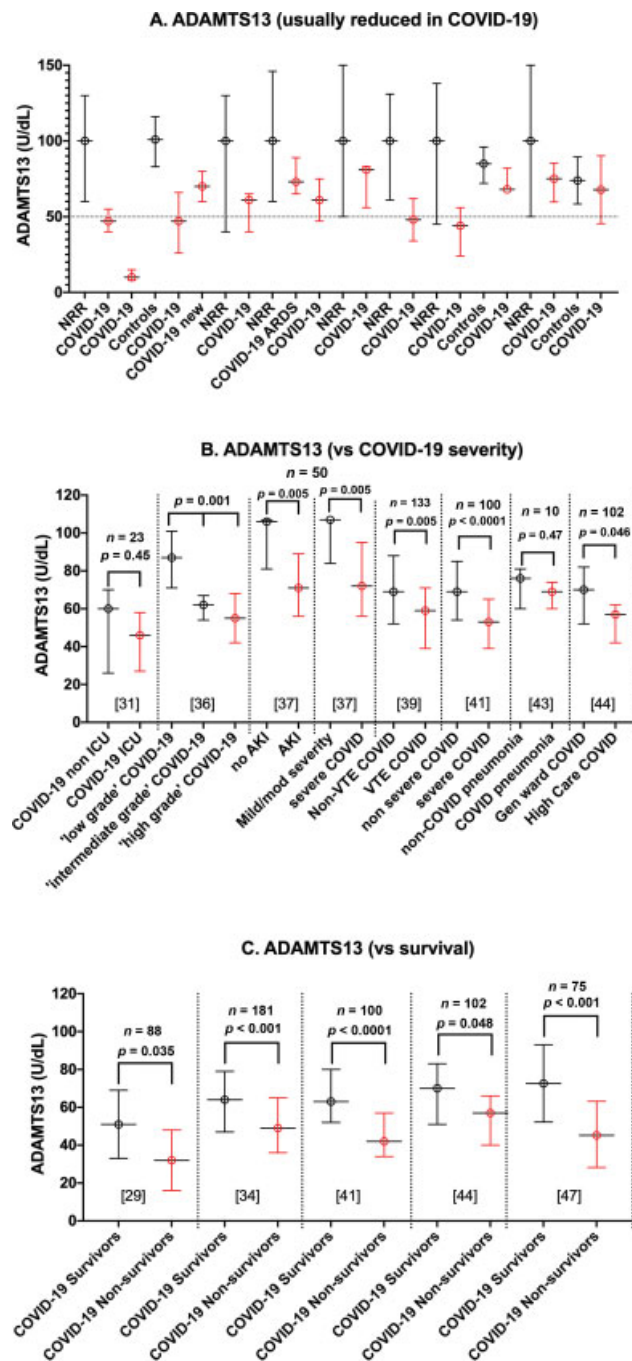


Fig. 5 Values of ADAMTS-13 activity reported in the literature for cases of coronavirus disease (COVID)-19, where more than five cases were reported. (A) ADAMTS-13 activity (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 (shown in red) versus normal reference ranges (NRRs) or control groups (shown in black). In general, NRRs were around 50–150 U/dL, whereas ADAMTS-13 in COVID-19 cases was generally lower, with some cases reporting <20 U/dL. (B) ADAMTS-13 activity (left Y-axis) in U/dL (= % of normal) for various cohorts of COVID-19 of differing “severity.” (C) ADAMTS-13 activity (left Y-axis) in U/dL (= % of normal) for survivor versus nonsurvivor cohorts of COVID-19. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; VTE, venous thromboembolism. Ranges are either median/interquartile range (IQR) or mean \pm standard deviation (SD)—as noted in **Tables 2** and **3**. References are given in square brackets. Numbers of cases and reported *p*-values are also given.

Perhaps relevant to the measurement of both VWF and ADAMTS-13 assays is the emergence of rapid assays by means of CLIA on the ACL AcuStar.^{49,54} Several studies reported on VWF and ADAMTS-13 using these methods (**Tables 1–3**), and it is likely that this technology will be increasingly used in the future.

Of interest, despite knowingly discussing raised VWF/ADAMTS-13 in COVID-19, very few studies actually reported ratio values (**Fig. 6**). In essence, this was also mirrored by limited reporting of VWF activity/Ag ratios (**Fig. 4**). We would therefore urge that future reports include mention of these ratio values, as this will considerably expand our understanding of the pathophysiology of COVID-19.

Irrespective of the earlier, the general increase in VWF to supranormal values in COVID-19, associated with a general decrease in ADAMTS-13 activity (even if remaining in the so-called NRR), would cause a general increase in VWF/ADAMTS-13 in the vast majority of studies, even if not numerically reported. The outcome of this increased VWF/ADAMTS-13 ratio essentially reflects an imbalance that creates a milieu that would favor (micro)thrombosis, similar to what might be seen in a secondary thrombotic microangiopathy.

In regard to thrombotic microangiopathy, the most severe form is represented by the condition of TTP, where ADAMTS-13 levels fall to below 10 U/dL (or %), although TTP may also be diagnosed where cases have ADAMTS-13 between 10 and 20 U/dL.⁵⁴ Very few reports in the literature actually report TTP in COVID-19. Most reports of COVID-19 report only moderately reduced levels of ADAMTS-13 (**Fig. 5**). Nevertheless, TTP or TTP-like syndromes have been reported in COVID-19. For example, Alharthy et al²⁷ reported a small case series of three cases of severe COVID-19 in which ADAMTS-13 was ≤ 15 U/dL (%). The patients were also reported to have antiphospholipid antibodies and presented clinically with stroke (brain infarction), respiratory distress syndrome, and pulmonary embolism. They were treated with plasma exchange, a treatment commonly applied in TTP, and patients improved clinically and gradually recovered neurologically (after 27–32 days). Another interesting case series was presented by Arulkumaran et al,³⁸ who utilized plasma exchange in seven severely critical COVID-19 patients with acute respiratory distress syndrome (ARDS) versus seven matched controls, and who not only showed improvement in patients after plasma exchange but also noted that five of seven controls developed AKI, whereas AKI was developed in none of the seven plasma-exchange-treated patients. The reported ADAMTS-13 levels in this case series were normal (median, 73 [IQR, 65–89] U/dL), but the median VWF/ADAMTS-13 ratio was high (4.0 [IQR, 2.8–5.7]). Thus, a therapy utilized in TTP may still have therapeutic success in COVID-19 without evidence of TTP. Finally, we can highlight the report from Doevelaar et al,⁴⁷ who concluded from their study that “COVID-19 is associated with a substantial increase in VWF levels, which can exceed the ADAMTS-13-processing capacity, resulting in the formation of large VWF multimers indistinguishable from TTP.”

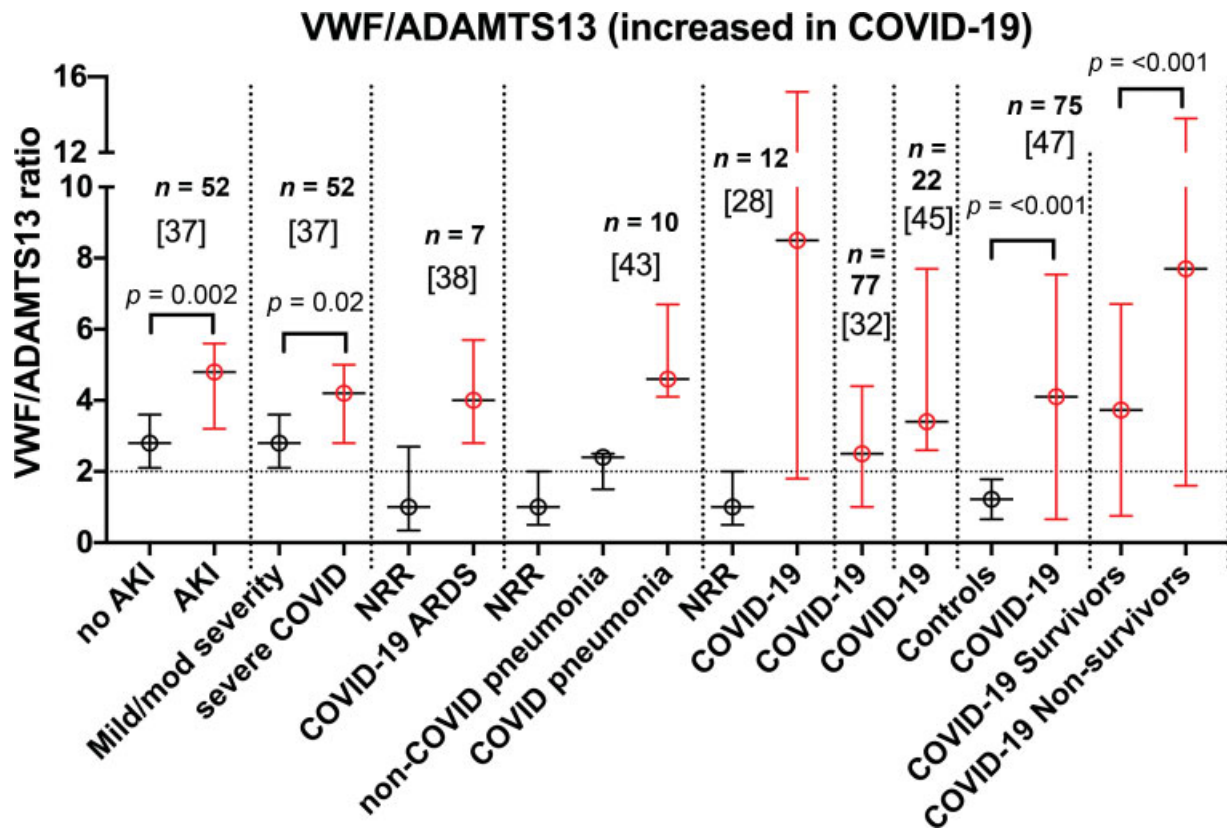


Fig. 6 Values of von Willebrand factor (VWF)/ADAMTS-13 ratio (Y-axis), as reported in the literature for cases of coronavirus disease (COVID)-19, where more than five cases reported. X-axis indicates study population for COVID-19, including grade of severity. References are given in square brackets. Numbers of cases and reported *p*-values are also given. Data have been converted to VWF/ADAMTS-13 where report gives as ADAMTS-13/VWF. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; NRR, normal reference range.

They investigated 75 patients with COVID-19 of varied severity *versus* 30 healthy controls. VWF:Ag in cases was high (mean \pm SD: 403 ± 218 vs. 99 ± 31 U/dL; $p < 0.001$). ADAMTS-13 levels in cases were only moderately (but not statistically) reduced (67.8 ± 22.4 vs. 73.9 ± 15.5 U/dL; $p = 0.176$). The ADAMTS-13/VWF ratio was significantly reduced (0.244 ± 20.5 vs. 0.820 ± 0.307 U/dL; $p < 0.001$, which is equivalent to a raised VWF/ADAMTS-13 ratio). Nevertheless, they also reported that large multimers in COVID-19 patients were significantly lower than in healthy pool samples ($68.69 \pm 16.16\%$ vs. $112.04 \pm 13.31\%$; $p < 0.0001$), which is counter-intuitive to what one may expect, but in essence similar to the finding reported by Mancini et al.³⁶ Such findings need future clarification, and appear to be at odds with the findings of Philippe et al.²² (as previously noted), who reported a higher proportion of HMW VWF in patients with critical COVID-19.

The number of cases as reported is another complication in the literature. We specifically excluded individual or small cases series (≤ 5) in our review of the literature shown in **Figs. 1–5 to 6**, but even the evaluated dataset had a significant variability in their sample size. Naturally, the larger the number, the more assurance on the findings.

A final complication of the literature that we will highlight is the disparity in reporting ranges and methods. Most studies reported study ranges as median/IQR; however, many alternatively reported mean/SD. A great variety of

VWF and ADAMTS-13 methods were also employed. Sometimes, methods could not be identified. We highlight the variety of methods has implications in regard to commutability of results. As an example, different methods yield different NRRs due to method and calibrator disparity. Different NRRs also imply different results would be expected between different methods for COVID-19 cases. The situation for VWF and ADAMTS-13 is in some respects similar to that previously raised for D-dimer.⁵⁵ We thus make the same call for investigators in the field to clearly report the methods utilized in future studies. We also call for investigators to report both VWF activity/Ag ratios and VWF/ADAMTS-13 ratios in future reports.

Conclusion

In summary, the current evidence strongly suggests that COVID-19 can progress toward a thrombotic disorder, characterized by both micro- and macrothrombosis in the lungs, as well as in many other organs and tissues.^{56–59} The development of any form of thrombosis will have a strong impact on a patient's prognosis, and appears in all severe COVID-19 patients to be accompanied by an imbalance of VWF and ADAMTS-13 resulting in a high VWF/ADAMTS-13 ratio. This may also pave the way to assessing specific therapies already used in secondary thrombotic microangiopathies, such as plasma exchange and complement

Table 3 Summary of literature related to VWF and ADAMTS-13 in COVID-19—Part III: (lowered) ADAMTS-13^a

Reference citation	Case descriptions and main findings	Number of COVID-19 cases	Data reporting	Method for ADAMTS-13	Link to COVID-19 severity
Martinelli et al ²⁵	Mild reduction of ADAMTS-13 activity (47 [40–55], normal range: 60–130) identified in 13 patients with COVID-19 hospitalized for respiratory symptoms with a chest X-ray compatible with bilateral interstitial pneumonia	13	Median? 95% CI	ADAMTS-13 method not specified	Not evaluated
Rovas et al ²⁶	23 hospitalized adult patients with moderate-to-severe or critical COVID-19. ADAMTS-13 decreased significantly with increasing COVID-19 severity (mechanical ventilation). Reduced ADAMTS-13 also associated with 60-day mortality	23	ADAMTS-13 reported in arbitrary units	ADAMTS-13 (multiplex assay)	ADAMTS-13 decreased significantly with increasing COVID-19 severity (mechanical ventilation). Reduced ADAMTS-13 also associated with 60-day mortality

Abbreviation: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; COVID, coronavirus disease; VWF, von Willebrand factor.

^aData exclude single case studies, and listed in order of PubMed listing. Note that wide variety of methods (not always documented) may be used to assess ADAMTS-13. This will have an influence on findings, but this is not always understood by authors who report on findings. Values reported in U/dL (= %).

inhibitors (e.g., eculizumab). Preliminary data suggest that use of complement inhibitors may be effective to improve survival and for reducing hypoxia, especially in COVID-19 patients with severe illness and/or ARDS.^{60–62} Similar promising results have been reported with plasma exchange.³⁸ These findings all suggest that secondary thrombotic microangiopathy may be a major driver of outcomes in SARS-CoV-2 infection, such that its attenuation by therapies already used in the treatment of thrombotic microangiopathy would appear a reasonable strategy.

Nevertheless, further research is needed to fully understand the mechanisms associated with the prothrombotic state in COVID-19, including how the VWF/ADAMTS-13 axis imbalance connects to the intermingled mechanisms of SARS-CoV-2 pathophysiology, such as immune dysregulation, complement overactivation, neutrophil extracellular traps, and autoantibodies, which may all converge to propagate COVID-19-associated coagulopathy.⁵⁶

Also, there needs to be improved reporting of VWF and ADAMTS-13 methodologies, which were not always described by researchers. This may be facilitated by a better understanding of how different VWF and ADAMTS-13 methodologies may lead to different NRRs and different values in COVID-19, and thus each study is not necessarily commutable to another study.

Conflict of Interest

None declared.

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