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Review Article

Prognostic value of von Willebrand factor and ADAMTS13 in patients with COVID-19: A systematic review and meta-analysis

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ABSTRACT

Background: Endotheliopathy and coagulopathy appear to be the main causes for critical illness and death in patients with coronavirus disease 2019 (COVID-19). The adhesive ligand von Willebrand factor (VWF) has been involved in immunothrombosis responding to endothelial injury. Here, we reviewed the current literature and performed meta-analyses on the relationship between both VWF and its cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) with the prognosis of COVID-19. **Methods:** We searched MEDLINE, Cochrane Library, Web of Science, and EMBASE databases from inception to 4 March 2022 for studies analyzing the relationship between VWF-related variables and composite clinical outcomes of patients with COVID-19. The VWF-related variables analyzed included VWF antigen (VWF:Ag), VWF ristocetin cofactor (VWF:Rco), ADAMTS13 activity (ADAMTS13:Ac), the ratio of VWF:Ag to ADAMTS13:Ac, and coagulation factor VIII (FVIII). The unfavorable outcomes were defined as mortality, intensive care unit (ICU) admission, and severe disease course. We used random or fixed effects models to create summary estimates of risk. Risk of bias was assessed based on the principle of the Newcastle-Ottawa Scale.

Results: A total of 3764 patients from 40 studies were included. The estimated pooled means indicated increased plasma levels of VWF:Ag, VWF:Rco, and VWF:Ag/ADAMTS13:Ac ratio, and decreased plasma levels of ADAMTS13:Ac in COVID-19 patients with unfavorable outcomes when compared to those with favorable outcomes (composite outcomes or subgroup analyses of non-survivor versus survivor, ICU versus non-ICU, and severe versus non-severe). In addition, FVIII were higher in COVID-19 patients with unfavorable outcomes. Subgroup analyses indicated that FVIII was higher in patients admitting to ICU, while there was no significant difference between non-survivors and survivors.

Conclusions: The imbalance of the VWF-ADAMTS13 axis (massive quantitative and qualitative increases of VWF with relative deficiency of ADAMTS13) is associated with poor prognosis of patients with COVID-19.

1. Introduction

The global pandemic of coronavirus disease 2019 (COVID-19) caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected tens of millions of people with the number of deaths growing exponentially [1,2]. The clinical manifestations of COVID-19 vary from asymptomatic or mild to severe acute respiratory distress syndrome (ARDS), multiple failure, and death [2,3]. One of the

clinical issues that rapidly became apparent is that thrombotic and microvascular complications are common in hospitalized patients with severe COVID-19 and non-survivors, despite standard thromboprophylaxis or therapeutic anticoagulation [4–6]. Both arterial thrombosis manifested in ischemic stroke and myocardial infarction, and venous thrombosis and thromboembolism, such as acute pulmonary embolism and deep vein thrombosis are frequently reported and associated with disease severity and prognosis [7–10]. Post-mortem histopathology has

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also shown widespread respiratory, cardiac, hepatic, and renal microthrombi in patients with COVID-19 [11–14]. However, this COVID-19-associated coagulopathy (CAC) have not yet been specifically defined. Available studies suggest that CAC develops at a relatively early stage, and is a mild form of sepsis-like diffuse intravascular coagulopathy (DIC) with increased levels of D-dimer and fibrinogen, relatively normal platelet count or mild thrombocytopenia, and near-normal/slightly prolonged prothrombin time (PT) and activated partial thromboplastin time [4,15,16]. However, DIC is a consumptive coagulopathy that is characterized by an increased D-dimer levels, decreased fibrinogen levels and platelet counts, and prolonged PT [17]. These distinct features suggest that CAC differs mechanistically from coagulopathy arising after other acute infections and common DIC. Several lines of evidence suggest the vascular events in COVID-19 patients appear to be mostly caused by in situ platelet-fibrin thrombus formation rather than embolic thrombi [12,18]. This widespread microvascular thrombi in multiple organs suggests that CAC resembles thrombotic microangiopathy (TMA) [19–21]. However, TMA-related hemolytic anemia and thrombocytopenia are relatively rare in patients with COVID-19 [22]. Hence, it is crucial to clearly define CAC and ascertain its underlying mechanisms.

Endothelial cell (EC) injury or dysfunction (endotheliopathy or endotheliitis) has emerged as the main cause of CAC, contributing to systemic inflammation, immune response, and hypercoagulability that predisposes thrombotic and microvascular events known as thromboinflammation or immunothrombosis [23–25]. Dupont et al. [24] demonstrated that endotheliopathy defined by the shedding of syndecan-1 is associated with respiratory failure, liver injury, multi-organ failure, and death of patients with COVID-19. von Willebrand factor (VWF) and its cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) play important roles in primary and secondary thrombotic, and inflammatory response to vascular injury [26–28]. An imbalanced VWF-ADAMTS13 axis has been implicated in pathologies like trauma [29–32], sepsis [33,34], malaria [35], preeclampsia [36,37], and ischemic stroke and myocardial infarction [38,39]. This imbalance has also been increasingly recognized for the development of complications of COVID-19 with increasing plasma VWF antigen and activity, and a generally reduction (or occasionally normal) of ADAMTS-13 activity [40,41], leading to kinetic deficiency of VWF cleavage. While recent meta-analyses confirmed that elevated VWF antigen (VWF:Ag) is associated with unfavorable outcomes of patients with COVID-19 [42,43], it is far less known regarding roles of other factors closely related to VWF biology, such as VWF release defined by VWF propeptide (VWFpp), adhesive activity (VWF ristocetin cofactor; VWF:Rco), multimer distribution, association with coagulation factor VIII (FVIII), and ADAMTS13 activity (ADAMTS13:Ac), in the development of COVID-19 complications. We therefore conducted a literature review and meta-analysis for information related to the association between VWF-related variables and outcomes in patients with COVID-19.

2. Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [44]. The pre-specified protocol for this meta-analysis has registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42021287385).

2.1. Search strategy and study selection

A comprehensive literature search was performed using MEDLINE (via PubMed), Cochrane Library, Web of Science, and the EMBASE databases from inception to March 4th, 2022. We searched for studies that investigated the plasma levels of VWF-related variables in patients with COVID-19 according to clinical outcomes using predefined keywords:

(“SARS-CoV-2” OR “COVID-19” OR “2019-nCoV” OR “Coronavirus disease 19”) AND (“von Willebrand Factor” OR “VWF” OR “von Willebrand” OR “Willebrand Protein”) AND (“ADAMTS13” OR “von Willebrand Factor cleaving proteinase”) AND (“Factor VIII” OR “FVIII”). The references listed in the retrieved articles were also reviewed to identify additional studies. Duplicate articles were removed after the initial search. Two reviewers (YJ and XZ) independently screened the title and abstract of the articles. The full-text of those that had passed the initial screening were assessed according to the eligibility criteria. Discrepancies were resolved by consensus between the two reviewers or by a third reviewer (XB) when a consensus could not be achieved.

2.2. Eligibility criteria

The inclusion criteria were as follows: 1) clinical trial or observational prospective/retrospective studies on COVID-19 with clinical outcomes for mortality (survivor vs. non-survivor), need for intensive care unit (ICU) admission (non-ICU vs. ICU), and severity (non-severe vs. severe); 2) reporting data on plasma levels of VWF:Ag, VWF:Rco, VWFpp, VWF multimer distribution, ADAMTS13:Ac, VWF:Ag/ADAMTS13:Ac ratio, and FVIII; 3) results were presented as or could be converted/digitized to standardized mean difference (SMD). The following types of articles were excluded from the analysis: case reports/series, brief reports, communications, correspondence, or letters that involved less than ten patients, review articles, commentaries, non-English language articles, research articles on the pediatric population, animal or in-vitro studies, unpublished studies, and studies with irrelevant or non-extractable results.

2.3. Data extraction

Two reviewers (YJ and XZ) extracted data from eligible studies independently using a predefined spreadsheet containing authors, country, publication date, study design, sample size, patient demographics, including age and gender, criteria used for clinical outcome classification, VWF related variable. The raw data were compared and pooled by the third investigator (XB) to eliminate extraction errors. The pooled effect estimates were SMD in terms of these variable between patients with and without poor clinical outcomes. When the data were expressed in median and quantiles, we derived and estimated the mean and standard deviation with accepted methods [45,46].

2.4. Quality assessment

Two reviewers (YJ and XZ) also independently assessed the risk of bias (methodological quality) for each included study based on the principle of the eight-item Newcastle-Ottawa Scale (NOS; for case-control study) [47] or revised NOS version (for cohort study; additional file 1) [48]. Studies with scores of 0–4 and 5–9 points were identified as low quality and high quality, respectively. Any disagreement was resolved by the two reviewers through discussion, if necessary, with the help of a third reviewer (XB). Funnel plots were used to assess the publication bias for outcomes that included more than ten studies.

2.5. Data synthesis and statistical analysis

The meta-analysis was conducted using the Review Manager software (RevMan5.3, Cochrane Collaboration, Oxford, UK). Continuous outcome variables were presented as SMD with 95 % confidence interval (CI). I-square (I^2) statistics was used to evaluate the data heterogeneity. Outcomes with $I^2 > 50\%$ were regarded as having a high heterogeneity. The random-effects model was used to analyze outcomes for included studies when $I^2 > 50\%$. Otherwise, a fixed-effect model was used. A p value of <0.05 was considered statistically significant in the test for overall effect. Publication bias was assessed by visualization of funnel

plots.

3. Results

3.1. Study selection and characteristics

A total of 1211 potentially relevant studies were included in the combined electronic and paper reference search. After removing 446 duplicates, 602 studies were excluded by title and abstract screening (reviews or not relevant). The final full-text review included 163 reports, from which 123 studies did not meet the inclusion criteria and were excluded. A total of 40 studies comprising of 3764 patients met the including criteria and were included in this systematic review and meta-analysis [24,49–87]. Fig. 1 shows the flow diagram of study selection. Table 1 presents study characteristics and patient demographics.

3.2. Meta-analysis of VWF-ADAMTS13 axis

We analyzed reported plasma levels of VWF:Ag, VWF:Rco, ADAMTS13:Ac, VWF:Ag/ADAMTS13:Ac ratio, and FVIII in patients with COVID-19. Since there were 2 studies that met the inclusion criteria having plasma VWFpp values [53,68] and 2 studies measured VWF multimeric pattern [68,76], these variables were not included in this meta-analysis.

3.2.1. VWF:Ag

A total of 33 studies comprising of 3377 patients were included. Plasma VWF:Ag levels were significantly higher in unfavorable outcomes than those with favorable outcomes (SMD = -0.95 95%CI [-1.15, -0.75], $p < 0.00001$; $I^2 = 81\%$; Fig. 2). Further analyses showed that COVID-19 patients with non-survivor status (SMD = -0.79 95%CI [-1.05, -0.52], $p < 0.00001$; $I^2 = 77\%$), ICU need (SMD = -0.96 95%CI [-1.30, -0.62], $p < 0.00001$; $I^2 = 61\%$) or high severity (SMD = -1.18 95%CI [-1.59, -0.77], $p < 0.00001$; $I^2 = 86\%$) had

higher plasma levels of VWF:Ag when compared to those with survivor status, non-ICU status, or low severity (Table 2 and Fig. S1).

3.2.2. VWF:Rco

A total of 8 studies comprising of 679 patients were included. The plasma levels of VWF:Rco, which measures the ability of VWF to agglutinate platelets, were significantly higher in patients with unfavorable outcomes than those with favorable outcomes (SMD = -0.83 95%CI [-1.33, -0.34], $p < 0.00001$; $I^2 = 87\%$; Fig. 3). They were also significantly higher in ICU-patients (SMD = -0.85 95%CI [-1.20, -0.50], $p < 0.00001$; $I^2 = 21\%$) and severe patients (SMD = -1.29 95%CI [-2.30, -0.29], $p = 0.001$; $I^2 = 91\%$) when compared to non-ICU-patients or non-severe patients (Table 2 and Fig. S2).

3.2.3. ADAMTS13:Ac

A total of 21 studies comprising of 2405 patients were included. Plasma levels of ADAMTS13:Ac was significantly lower in patients with unfavorable outcomes than those with favorable outcomes (SMD = 0.78 95%CI [0.60, 0.95], $p < 0.00001$; $I^2 = 63\%$; Fig. 4). The subgroup analyses (Table 2 and Fig. S3) further showed statistically significant differences between survivors and non-survivors (SMD = 0.78 95%CI [0.57, 1.00], $p < 0.00001$; $I^2 = 55\%$), ICU admission and non-ICU admission (SMD = 0.72 95%CI [0.31, 1.13], $p = 0.0006$; $I^2 = 60\%$), and severe status and non-severe status (SMD = 0.76 95%CI [0.34, 1.19], $p = 0.0004$; $I^2 = 77\%$).

3.2.4. VWF:Ag/ADAMTS13:Ac ratio

A total of 11 studies comprising of 1286 patients were included. The ratio of VWF:Ag to ADAMTS13:Ac was significantly higher in patients with unfavorable outcomes than those with favorable outcomes (SMD = -0.94 95%CI [-1.24, -0.65], $p < 0.00001$; $I^2 = 76\%$; Fig. 5). A higher VWF:Ag/ADAMTS13:Ac ratio was also associated to the non-survivor status (SMD = -0.85 95%CI [-1.36, -0.33], $p = 0.001$; $I^2 = 82\%$), ICU admission (SMD = -0.96 95%CI [-1.27, -0.64], $p < 0.00001$; $I^2 =$

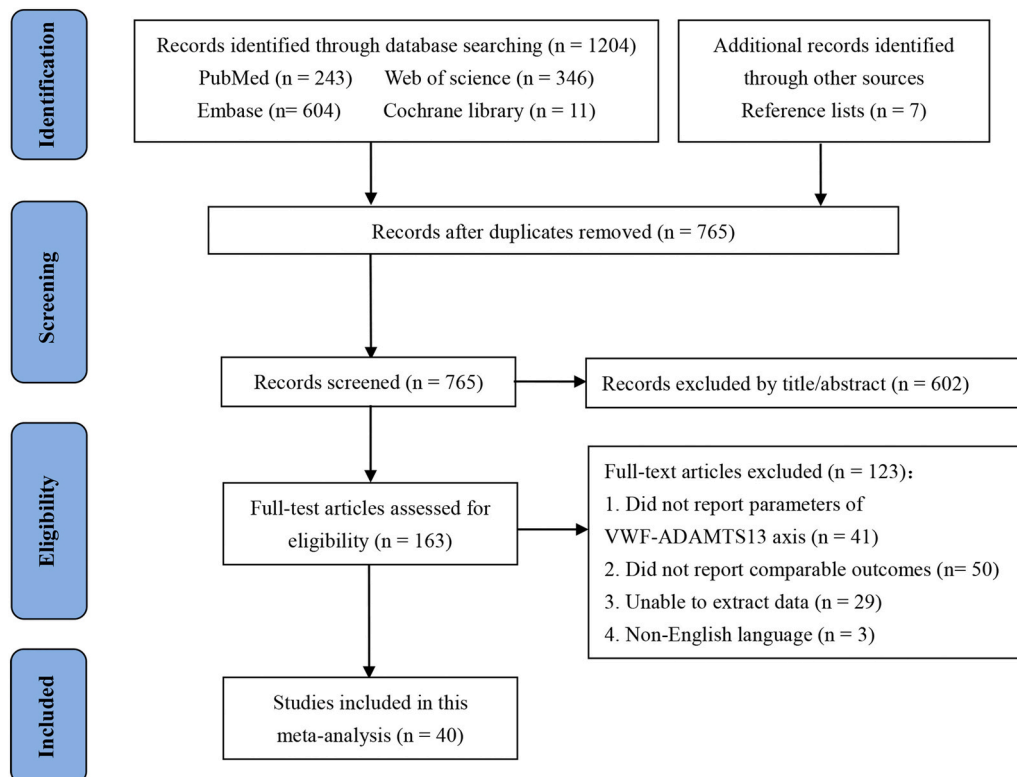


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1
Characteristics of the included studies.

Study	Country	Design	Period	Total				Favorable clinical outcomes			Unfavorable clinical outcomes			VWF-related variables	Quality (NOS)
				Size	Age (year)	Gender, n (Female/Male)	Endpoints	Size	Age (year)	Gender, n (Female/Male)	Size	Age (year)	Gender, n (Female/Male)		
Bauer et al.	Germany	Prospective; Single center	March 2020–June 2020	17	70.1 (IQR, 55.6–72.0)	11/6	ICU admission	10	63.7 (IQR, 52.5–71.0)	6/4	7	71.9 (IQR, 57.5–76.8)	5/2	VWF: Ag; VWF: Rco	8
Bazzan et al.	Italy	Retrospective; Single center	N/A	88	N/A	N/A	Mortality	79	59.37 ± 12.7	25/54	9	71.89 ± 7.1	3/6	VWF: Ag; ADAMTS13: Ac	7
Blasi et al.	Spain	Prospective; Single center	April 2020	23	64 (IQR, 53–74)	9/14	ICU admission	11	58 (IQR, 42–74)	3/8	12	69 (IQR, 57–76)	6/6	VWF: Ag; ADAMTS13: Ac; FVIII	7
Cugno et al.	Italy	Prospective; Single center	March 1, 2020–April 15, 2020	104	N/A	N/A	Severity	58	N/A	N/A	46	N/A	N/A	VWF: Ag	7
De Jongh et al.	Netherlands	Cross-sectional; Single center	N/A	16	N/A	N/A	Mortality	11	62.5 ± 13.7	N/A	5	78.0 ± 6.4	N/A	VWF: Ag; ADAMTS13: Ac; FVIII	5
Delrue et al.	France	Prospective; Single center	March 17, 2020–11 April 2020	133	65 (IQR, 56–75)	97/26	Mortality	110	N/A	N/A	23	N/A	N/A	ADAMTS13: Ac	5
Doevelaar et al.	Germany	Prospective; Single center	N/A	75	66 ± 16	38/37	Mortality	62	N/A	N/A	13	N/A	N/A	VWF: Ag/ADAMTS13 ratio; ADAMTS13: Ac	6
Dupont et al.	France	Prospective; Single center	March 21, 2020–April 16, 2020	82	60 ± 14	18/64	Mortality	60	N/A	N/A	22	N/A	N/A	VWF: Ag	9
Dushianthan et al.	GBR	Retrospective; Single center	March 2020–March 2021	65	N/A	N/A	Mortality	54	N/A	N/A	11	N/A	N/A	VWF: Ag; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio; FVIII	7
Fan et al.	Singapore	Prospective; Multi-center	June 2020–January 2021	20	60 (IQR, 49.5–64.5)	4/16	Severity	10	60 (IQR, 50–65)	2/8	10	60 (IQR, 49–64)	2/8	VWF: Ag; FVIII	8
Fernández et al.	Spain	Prospective; single center	May 1, 2020–May 31, 2020	34	N/A	N/A	Severity	24	53 (IQR, 43–71)	10/14	10	66 (IQR, 52–75)	3/7	VWF: Ag; ADAMTS13: Ac	7
Francischetti et al.	United States	Cross-sectional; Single center	April 2020–October 2020	66	N/A	33/33	Severity	40	47 (IQR, 22–65.2)	21/19	26	66 (IQR, 34–78)	12/14	VWF: Ag; VWF: Ac; ADAMTS13: Ac	7
Goshua et al.	United States	Cross-sectional; Single center	April 13, 2020–April 24, 2020	68	62 ± 16	27/41	ICU admission	20	58 ± 15	15/33	48	64 ± 16	12/8	VWF: Ag; FVIII	7
Helin et al.	Finland	Retrospective; Single center	April 2020–May 2020	78	56 (Range, 16–87)	34/44	ICU admission	44	N/A	23/21	34	N/A	11/23	FVIII	5
Henry et al.	United States	Prospective; Single center	April 2020–May 2020	52	51 (IQR, 39–66)	22/30	Severity	36	N/A	N/A	16	N/A	N/A	VWF: Ag; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio	6
Herr et al.	Germany	Prospective; Multi-center	March 2020–July 2020	35	63.86 ± 3.18	9/26	Mortality	24	61.96 ± 4.3	N/A	11	68.27 ± 3.72	N/A	VWF: Ag	7
Joly et al.	France	Prospective; Single center	March 18, 2020–May 9, 2020	53	59 (IQR, 53–66)	14/39	Mortality	38	60 (IQR, 50–64)	12/26	15	58 (IQR, 56–67)	2/13	VWF: Ag; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio	7

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Table 1 (continued)

Study	Country	Design	Period	Total				Favorable clinical outcomes			Unfavorable clinical outcomes			VWF-related variables	Quality (NOS)
				Size	Age (year)	Gender, n (Female/Male)	Endpoints	Size	Age (year)	Gender, n (Female/Male)	Size	Age (year)	Gender, n (Female/Male)		
Jothimani et al	India	Prospective; Single center	July 1, 2020- July 12, 2020	35	50 (IQR, 44.5–55.7)	13/22	ICU admission	27	N/A	N/A	8	N/A	N/A	VWF: Ag	6
Lichter et al.	Israel	Retrospective; Single center	March 10, 2020- April 26, 2020	39	N/A	N/A	ICU admission	5	N/A	N/A	34	57 (Range, 22–76)	10/24	FVIII	7
Lopez-Castaneda et al.	Mexico	Prospective; Single center	January 5, 2021- February 4, 2021	55	N/A	N/A	Severity	37	44.52 ± 12.7	11/26	18	63.77 ± 13.8	9/9	VWF: Ag	8
Mancini et al.	Italy	Retrospective; Single center	March 2020-mid-April 2020	33	N/A	N/A	Severity	14	58 (Range, 27–85)	7/7	19	59 (Range, 40–71)	6/13	VWF: Ag; VWF: Ac; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio	7
Marchetti et al.	Italy	Prospective; Single center	March 23, 2020- May 30, 2020	63	62 (Range 35–88)	18/45	Mortality	50	N/A	N/A	13	N/A	N/A	VWF: Ag; VWF: Rco	7
Marco et al.	Spain	Prospective; single center	April 2020- May 2020	152	N/A	N/A	Mortality	143	N/A	N/A	9	N/A	N/A	VWF: Ag; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio	6
Martín-Rojas et al.	Spain	Retrospective; Single center	April 2020	62	61.8 ± 15.2	10/43	Mortality	51	61.2 ± 15.4	16/35	11	64.7 ± 14.9	3/8	VWF: Ag; ADAMTS13: Ac; FVIII	8
Martín-Rojas et al.	Spain	Retrospective; Single center	April 3, 2020–May 3, 2020	206	63.6 ± 13.4	75/131	Mortality	188	62.4 ± 12.9	68/120	18	76.0 ± 12.3	7/11	FVIII	7
Montiel et al.	Belgium	Prospective; Single center	April 27, 2020–November 3, 2020	60	N/A	13/47	ICU admission	180	64.22 ± 13.84	67/113	26	59.9 ± 9.55	8/18	VWF: Ag; VWF: Rco; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio	8
Montiel et al.	Belgium	Prospective; Single center	April 27, 2020–November 3, 2020	60	N/A	13/47	ICU admission	30	52.1 ± 13.5	8/22	30	61.3 ± 8.7	5/25	VWF: Ag; VWF: Rco; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio	8
Nougier et al.	France	Prospective; Single center	N/A	78	60.2 ± 14.4	27/51	ICU admission	30	60.2 ± 14.6	N/A	48	62.8 ± 13.1	N/A	FVIII	8
Pascreau et al.	France	Prospective; Single center	N/A	70	N/A	N/A	Mortality	55	N/A	N/A	15	N/A	N/A	VWF: Ag	6
Philippe et al.	France	Prospective; Multi-center	March 13, 2020- June 26, 2020	66	N/A	N/A	ICU admission	44	N/A	N/A	22	N/A	N/A	VWF: Ag	6
Philippe et al.	France	Prospective; Multi-center	March 13, 2020- June 26, 2020	185	N/A	N/A	Severity	96	65.5 (IQR, 55.0–76.0)	41/55	89	62.0 (IQR, 51.0–71.0)	24/65	VWF: Ag; VWF: Rco	8
Philippe et al.	France	Cross-sectional; Single center	N/A	77	N/A	N/A	Severity	37	63 (IQR, 52–72)	12/25	40	62 (IQR, 53–72)	7/33	VWF: Ag; ADAMTS13 ratio	7
Rauch et al.	France	Prospective; Single center	March 20, 2020- April 17, 2020	243	63.9 ± 16.2	88/155	Mortality	211	N/A	N/A	32	N/A	N/A	VWF: Ag; FVIII	8
Rodríguez et al.	France	Retrospective; Single center	March 15, 2020- April 1, 2020	100	60.5	30/70	Mortality	81	N/A	N/A	19	N/A	N/A	VWF: Ag; ADAMTS13: Ac	7
Sinkovits et al.	Hungary	Prospective; Single center	April 20, 2020- July 2, 2020	102	67 (IQR, 56–76)	46/56	Severity	50	N/A	N/A	50	N/A	N/A	VWF: Ag; ADAMTS13: Ac	7
Sinkovits et al.	Hungary	Prospective; Single center	April 20, 2020- July 2, 2020	102	67 (IQR, 56–76)	46/56	Mortality	77	N/A	N/A	25	N/A	N/A	VWF: Ag; ADAMTS13: Ac	7
Sinkovits et al.	Hungary	Prospective; Single center	April 20, 2020- July 2, 2020	102	67 (IQR, 56–76)	46/56	Severity	60	N/A	N/A	42	N/A	N/A	ADAMTS13: Ac	7

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Table 1 (continued)

Study	Country	Design	Period	Total			Endpoints	Favorable clinical outcomes			Unfavorable clinical outcomes			VWF-related variables	Quality (NOS)
				Size	Age (year)	Gender, n (Female/Male)		Size	Age (year)	Gender, n (Female/Male)	Size	Age (year)	Gender, n (Female/Male)		
Sweeney et al.	United States	Retrospective; Single center	March 26, 2020–May 5, 2020	181	N/A	N/A	Mortality	91	62.0 (IQR, 50.5–70.0)	45/46	90	72.5 (IQR, 63.3–79.8]	30/60	VWF: Ag/ADAMTS13 ratio VWF: Ag; VWF: Rco; ADAMTS13: Ac; FVIII	8
Thangaraju et al.	United States	Retrospective; Single center	April 14, 2020–May 31, 2020	543	63 (Range, 3.0–99)	N/A	Mortality	433	N/A	N/A	110	N/A	N/A	VWF: Ag; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio; FVIII	6
Thomas et al.	India	Prospective; Single center	July 22, 2020–August 3, 2020	71	N/A	N/A	Severity	34	35.5 (IQR, 29–49)	12/22	37	57 (IQR, 49–62)	3/34	VWF: Ag	6
Tiscia et al.	Italy	Prospective; Single center	March 12, 2020–September 30, 2020	74	68.0 (IQR, 22.0)	43	ICU admission	52	69.0 (IQR, 19.7)	26/26	22	63.0 (IQR, 15.2)	5/17	VWF: Ag; VWF: Rco; ADAMTS13: Ac; VWF: Ag/ADAMTS13 ratio; FVIII	7
Torres-Ruiz et al.	Mexico	Prospective; Single center	March 2020–August 2020	70	N/A	N/A	Severity	34	34.00 (IQR, 27.25–43.00)	15/19	36	54.50 (IQR, 46.75–60.75)	6/30	VWF: Ag	7
Vassiliou et al.	Greece	Prospective; Single center	March 22, 2020–October 25, 2020	38	63 ± 11	7/31	Mortality	28	62 ± 11	5/23	10	68 ± 10	2/8	VWF: Ag	9
von Meijenfildt et al.	Sweden	Prospective; Single center	April 9, 2020–June 8, 2020	102	N/A	N/A	Mortality	92	N/A	N/A	10	N/A	N/A	VWF: Ag; ADAMTS13: Ac; FVIII	7

Abbreviations: ADAMTS13: Ac, a disintegrin and metalloprotease with thrombospondin type I repeats, member 13: Activity; CI, confidence interval; FVIII, factor VIII; ICU, intense care unit; IQR, interquartile range; NOS, Newcastle-Ottawa Scale; VWF, von Willebrand factor; VWF: Ag, VWF antigen; VWF: Rco, VWF ristocetin cofactor.

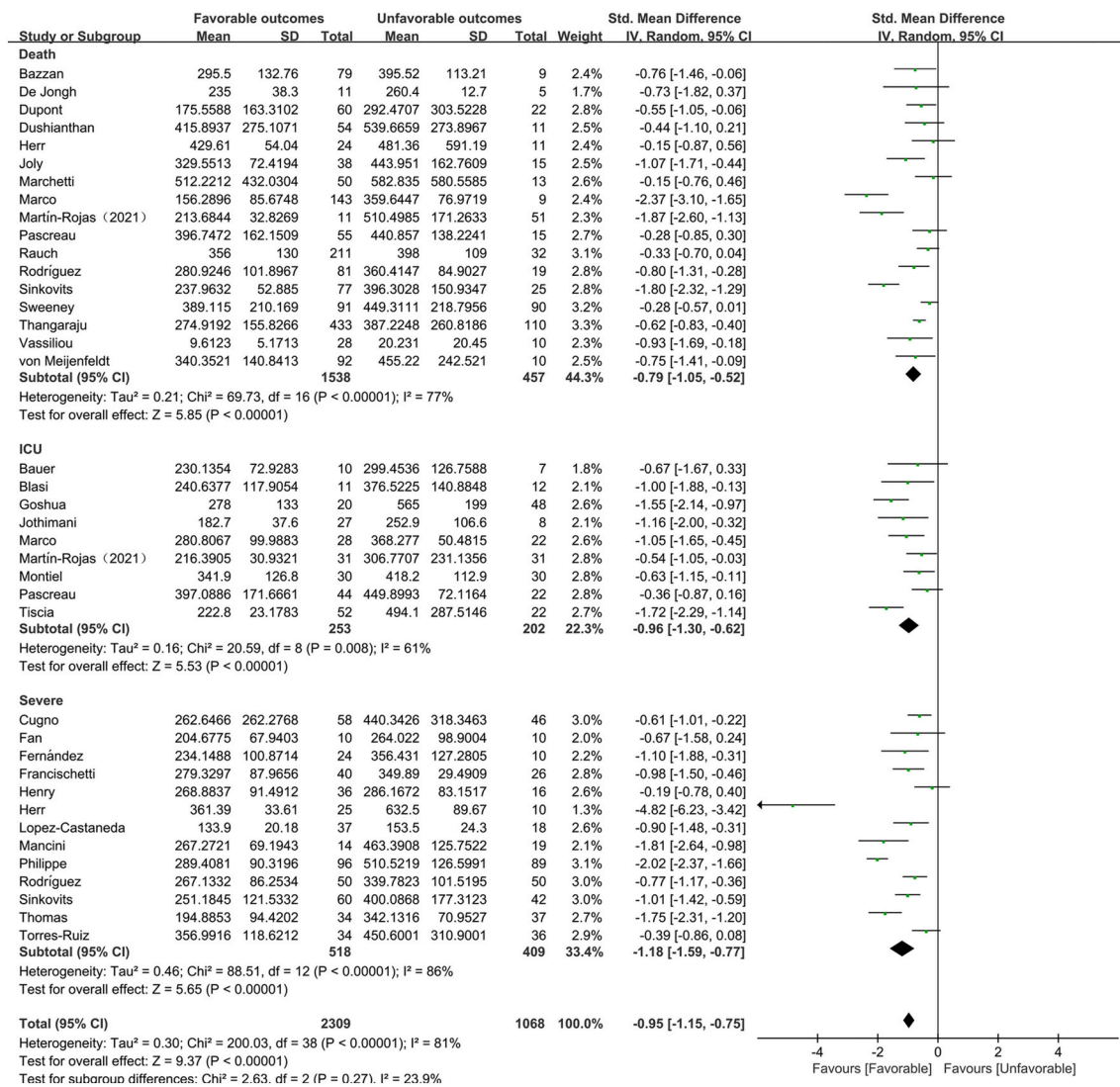


Fig. 2. Forest plot of the association between VWF:Ag and composite clinical outcomes.

0 %), and severe disease (SMD = -1.06 95%CI [-1.61, -0.52], p = 0.0001; I² = 74 %) (Table 2 and Fig. S4).

3.2.5. FVIII

A total of 15 studies comprising of 1970 patients were included. The plasma levels of FVIII were significantly higher in patients with unfavorable outcomes than those with favorable outcomes (SMD = -0.69 95%CI [-1.05, -0.33], p = 0.0002; I² = 88 %; Fig. 6). Subgroup analyses (Table 2 and Fig. S5) further showed that plasma FVIII levels were significantly higher in COVID-19 patients who were admitted to ICU (SMD = -0.81 95%CI [-1.15, -0.47], p < 0.00001; I² = 67 %), while there was no significant difference between non-survivors and survivors (SMD = -0.62 95%CI [-1.27, 0.04], p = 0.06; I² = 93 %).

3.3. Publication bias

All included studies were assessed with 5 to 9 points (Table 1). The funnel plot was used to assess the publication bias for endpoint measures which pooled more than ten studies. No apparent publication bias was found in all the eligible endpoints. The funnel plots were listed in the supplement Fig. S6.

4. Discussion

This meta-analysis found a significant association between imbalanced VWF-related variables (massive quantitative and qualitative increases of VWF with relative deficiency of ADAMTS13) and outcomes in patients with COVID-19. However, the question remains as whether these VWF-related variables should be considered as an independent entity or part of CAC.

4.1. COVID-19-associated endotheliopathy and coagulopathy

CAC was first described by Tang et al. in a single-center study in Wuhan, China [4]. Autopsy results from COVID-19 deaths have consistently highlighted the marked endotheliopathy, which is characterized with EC desquamation, cytoplasmic vacuolization, swelling, tight junction disruption, and loss of contact with the basilar membrane in the lung, heart, brain, mesentery, and kidney [88,89]. Recent evidence suggests that endotheliopathy contributes to hyperinflammatory and hypercoagulable states that predispose COVID-19 patients to thrombosis and microvascular events [23–25]. Won et al. [90] reported the upregulated pro-coagulants, downregulated anti-coagulants and severe thrombosis, and infiltration of activated macrophages, monocytes, and T cells within autopsy lungs of COVID-19 patients. Ranucci et al. [91] demonstrated a closely correlation between interleukin (IL)-6 and

Table 2
Summary of stratified subgroup analysis of VWF-ADAMTS13 axis-related parameters between unfavorable and favorable clinical outcomes.

VWF: Ag							
Endpoints	Number of studies included	Favorable clinical outcomes (total patients, n)	Unfavorable clinical outcomes (total patients, n)	Total patients, n	Standard mean difference, 95%CI	P value	I ²
Mortality	17	1538	457	1995	-0.79 [-1.05, -0.52]	p < 0.00001	77 %
ICU admission	9	253	202	455	-0.96 [-1.30, -0.62]	p < 0.00001	61 %
Severity	13	518	409	927	-1.18 [-1.59, -0.77]	p < 0.00001	86 %
VWF: Rco							
ICU admission	3	92	59	151	-0.85 [-1.20, -0.50]	p < 0.00001	21 %
Severity	3	150	134	284	-1.29 [-2.30, -0.29]	p = 0.001	91 %
ADAMTS13: Ac							
Mortality	13	1322	350	1672	0.78 [0.57, 1.00]	p < 0.00001	55 %
ICU admission	5	152	117	269	0.72 [0.31, 1.13]	p = 0.0006	60 %
Severity	7	261	203	464	0.76 [0.34, 1.19]	p = 0.0004	77 %
VWF: Ag/ADAMTS13: Ac Ratio							
Mortality	5	664	174	838	-0.85 [-1.36, -0.33]	p = 0.001	82 %
ICU admission	3	110	74	184	-0.96 [-1.27, -0.64]	p < 0.00001	0 %
Severity	4	147	117	264	-1.06 [-1.61, -0.52]	p = 0.0001	74 %
FVIII							
Mortality	8	1067	255	1322	-0.62 [-1.27, -0.04]	p = 0.06	93 %
ICU admission	8	373	255	628	-0.81 [-1.15, -0.47]	p < 0.00001	67 %

Abbreviations: ADAMTS13: Ac, a disintegrin and metalloprotease with thrombospondin type I repeats, member 13: Activity; CI, confidence interval; FVIII, factor VIII; ICU, intense care unit; VWF, von Willebrand factor; VWF: Ag, VWF antigen; VWF: Rco, VWF ristocetin cofactor.

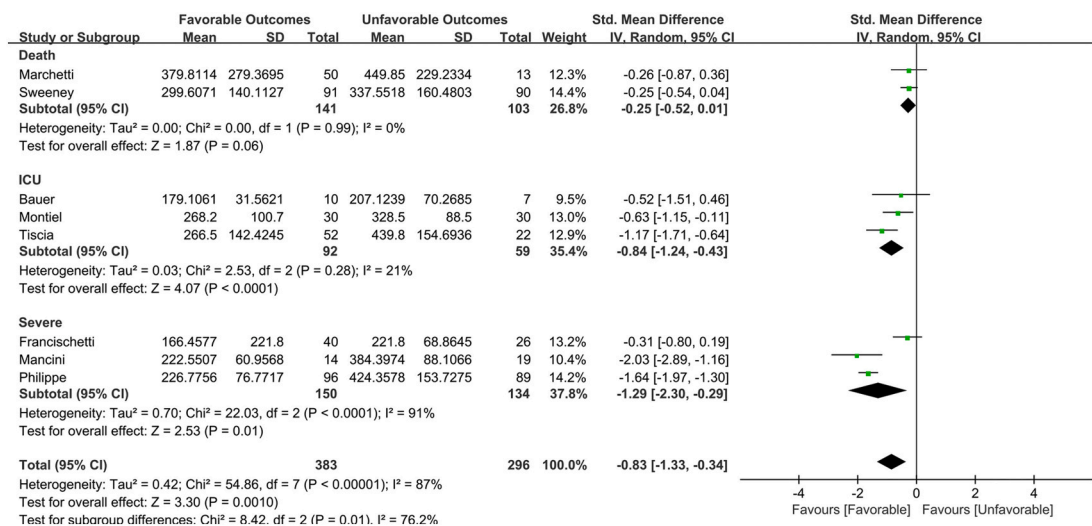


Fig. 3. Forest plot of the association between VWF:Rco and composite clinical outcomes.

fibrinogen in patients with COVID-19. A correlation between inflammatory cytokines and VWF was also reported by Dupont and colleagues [24]. The coordinated activation of the inflammatory and thrombotic responses is now termed immunothrombosis (or thromboinflammation),

whereby COVID-19 induces endothelial injury, immune dysregulation, and inflammation, with resultant thrombosis and further propagation of inflammation [92,93]. Ciceri et al. [94] thus recommended the use of MicroCLOTS (microvascular COVID-19 lung vessels obstructive

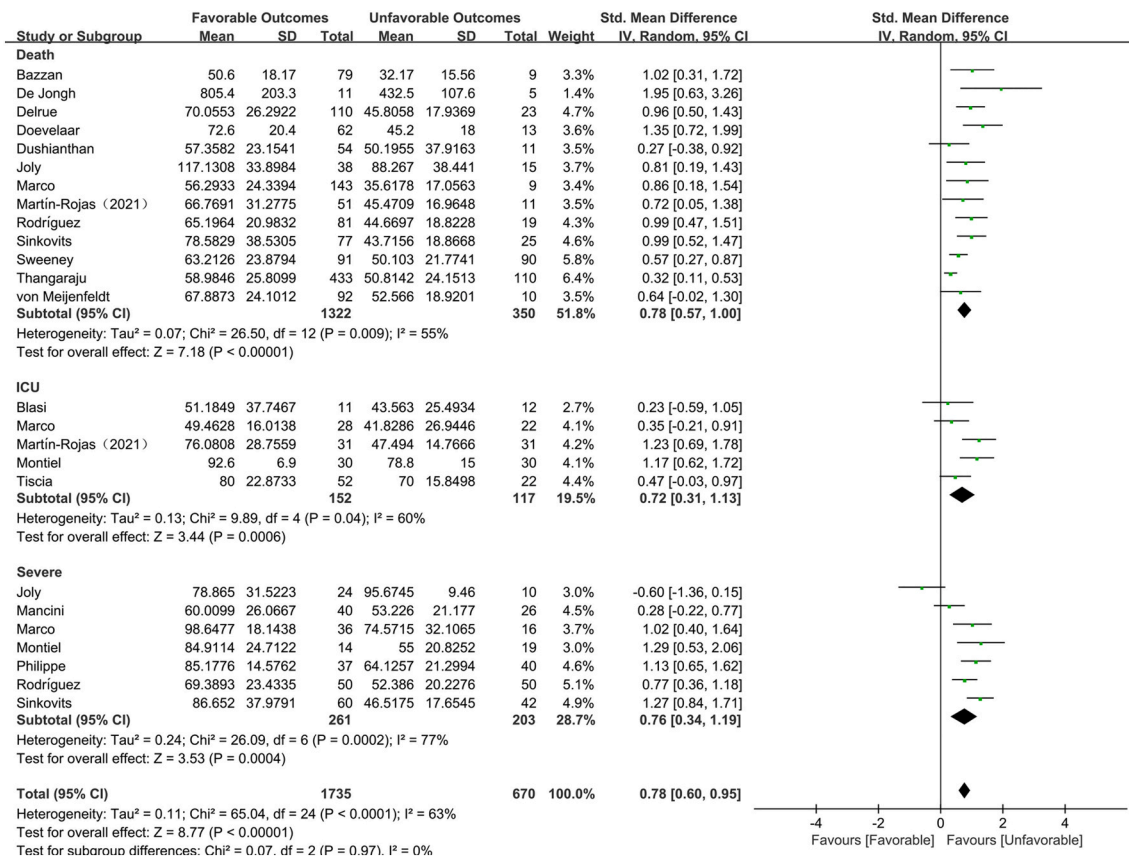


Fig. 4. Forest plot of the association between ADAMTS13:Ac and composite clinical outcomes.

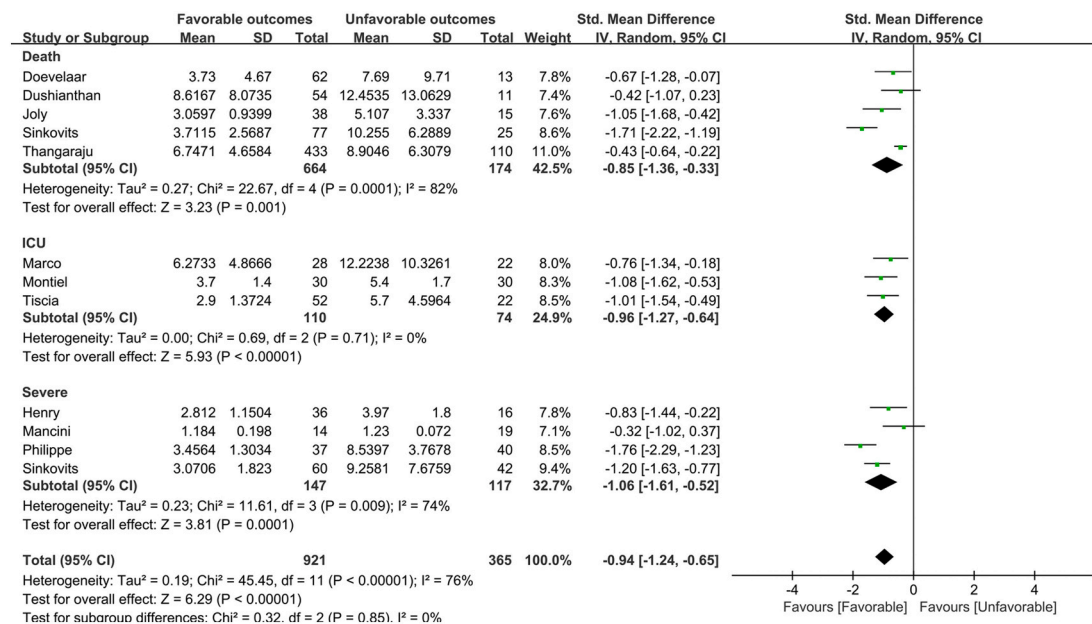


Fig. 5. Forest plot of the association between VWF:Ag/ADAMTS13:Ac ratio and composite clinical outcomes.

thromboinflammatory syndrome) to define thromboinflammatory response to COVID-19. A prevalent view holds that SARS-CoV-2 enters ECs directly by binding to the transmembrane angiotensin-converting enzyme 2 (ACE2) receptor [89,95,96]. But more recent studies have disputed the expression of ACE2 on ECs in postmortem COVID-19 tissues and in cultured ECs, and they suggest that the endotheliopathy is

induced by pro-inflammatory cytokine milieu, complement activation, or tissue hypoxia [90,97–99]. Ma et al. [100] recently reviewed and summarized that ROS, VEGFA/VEGFR2, and HMGB1/RAGE/TLR4 are potential signaling pathways that involved in the COVID-19-associated endotheliopathy. These findings explain why patients with conditions of systemic endotheliopathy, such as cardiovascular disease, diabetes

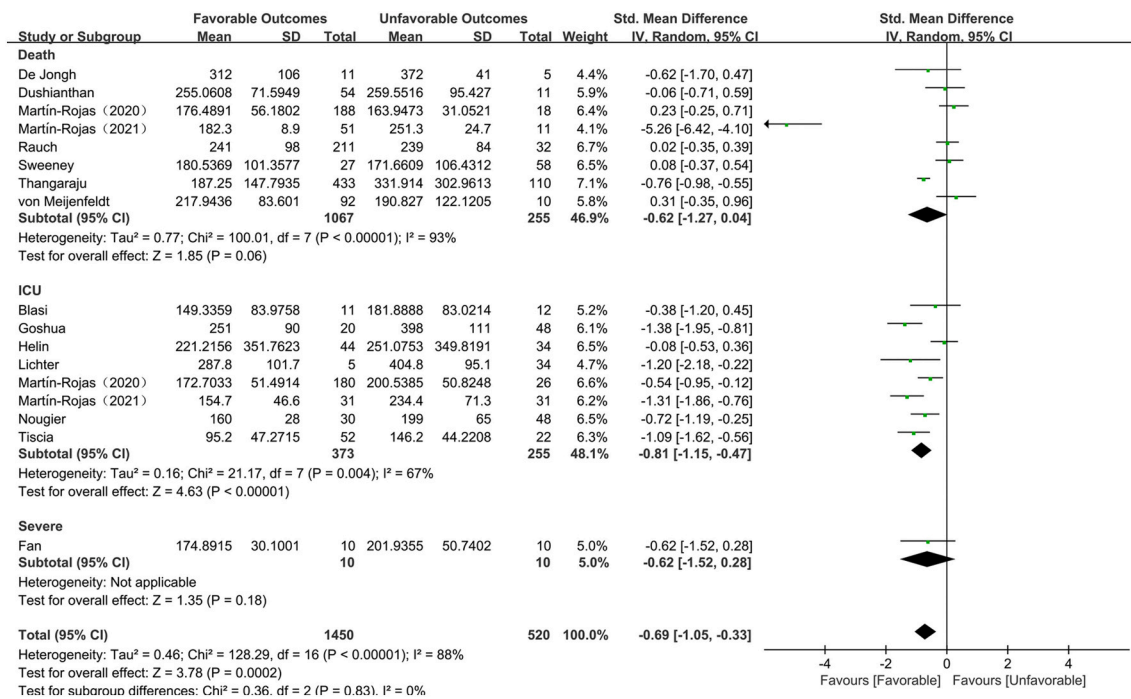


Fig. 6. Forest plot of the association between FVIII and composite clinical outcomes.

mellitus, chronic kidney disease, and cancer, are at a higher risk for severe COVID-19. It is therefore also not surprisingly that endotheliopathy and resultant CAC are more severe in the elderly with preexisting comorbidities [101–105]. An interesting question is as whether individuals on anti-platelet or anti-coagulant regimens for other conditions are less vulnerable for more severe COVID-19. Although D-dimer and fibrinogen are recognized to be related to thrombotic risk in COVID-19 early during the pandemic [16]. Circulating soluble biomarkers associated with endotheliopathy, including syndecan-1, VWF, selectins P and E, and intercellular adhesion molecule-1 (ICAM-1) have emerged as more clinically relevant biomarkers of CAC, multi-organ failure, and disease severity [42,86,106,107]. However, whether these variables can be used for prospective clinical assessments may require further studies [106].

4.2. VWF-ADAMTS13 axis in COVID-19-associated endotheliopathy and coagulopathy

VWF is a large multimeric glycoprotein encoded by the VWF gene on the short arm of chromosome 12, and is synthesized primarily in ECs and megakaryocytes [108,109]. The architecture of pro-VWF composes four types of domains that are constructed as repeats in the following order: D1-D2-D'-D3-A1-A2-A3-D4-C1-C2-C3-C4-C5-C6-CK. The D1-D2 domains represent VWFpp that is cleaved off by furin, and the D'-CK represents mature VWF monomer. Mature VWF and VWFpp are secreted in equimolar amounts from ECs into plasma [110]. Upon synthesis, VWF is either secreted constitutively as smaller multimers (basal secretion), or stored in Weibel-Palade bodies (WPBs) of ECs and α-granules of platelets where multimerization continues [large and ultra-large VWF (ULVWF)] and release occurs upon various pathological stimuli (regulated release) [109,111]. The majority of circulating VWF (80–90 %) in blood is derived from ECs, and it is therefore frequently used as a biomarker for endothelial activation or injury [26,109]. Autopsy results reveal that VWF expression was increased in ECs of the lung, heart, and kidney from COVID-19 patients [90]. Babkina et al. [112] found more intensive VWF immunostaining in pulmonary ECs of COVID-19 patients with thrombotic complications than those without thrombotic complications. Moreover, platelet-VWF plug formation was present within the

pulmonary microcirculation of patients with COVID-19 [13,24]. Several studies have reported elevated plasma levels of VWF:Ag in patients with COVID-19 compared with healthy controls, which confirmed a severe inflammatory state and fulminant endotheliopathy [51,52,55,59,63,67,70,75,87,113]. In addition, several studies found increased levels of VWFpp in patients with COVID-19, however, this increase was less pronounced than that of VWF:Ag. They assumed that the decreased ratio of VWFpp to VWF:Ag indicated a diminished clearance of VWF. Although the mechanism is unclear, this may further contribute to the markedly increased VWF:Ag [53,68,114,115]. However, whether the increase in VWF is the result of increased production, WPB exocytosis, or decreased clearance remains to be determined. Here, we indicated that levels of VWF:Ag were higher in patients with poor prognosis, consistent with those of two previous meta-analyses that included 10 studies/996 patients and 7 studies/695 patients, respectively [42,43]. Notably, Ward et al. [114] reported that elevated VWF:Ag was persisted during 3-week ICU stay, suggesting the sustained synthesis and release of VWF. The “post-acute COVID-19 syndrome”, which is defined as having dyspnea, fatigue, sleep disorder, and exercise intolerance following acute COVID-19 resolution, has also been attributed to persistent endotheliopathy [115,116]. Levels of plasma VWF:Ag and VWFpp remained persistently high in some convalescent COVID-19 patients [115,117], and were correlated with elevated D-dimer levels [115]. The mechanisms underlying these persistent endotheliopathy after recovery from COVID-19 remain poorly understood. It is worth noting that ECs of pulmonary small vessels and microvessels express 5–50 times higher concentrations of VWF mRNA than similar sized vessels in the kidney and liver [118]. Another interesting observation is that a greater absolute increase in VWF:Ag than FVIII (mainly synthesized in hepatocytes [119]) in COVID-19 patients [78,114]. These may highlight the predominantly pulmonary-centric nature of COVID-19 and the critical roles of VWF in the pathophysiology of COVID-19.

Upon vascular injury, VWF undergo conformational changes that expose the functional A1 domain, which is hidden in a globular structure by forming a complex with the adjacent A2 domain, facilitating 1) binding of platelets to subendothelium under blood flow through its interactions with platelet receptor glycoprotein (GP)Ibα (via A1 domain) and subendothelial collagen (via A3 domain); 2) platelet-platelet

interaction (platelet aggregation) by binding to platelet receptor GPIIb/IIIa, thereby inducing hemostatic plug formation (primary haemostasis) [120,121]. VWF also serves as chaperone for FVIII (via D'-D3 domain), 1) protecting FVIII from enzymatic degradation and extending its half-life in blood; more importantly; 2) directing its localization to the site of vascular injury and promoting coagulation cascades (secondary haemostasis) [120,121]. The ULVWF freshly released from activated ECs, either circulating in plasma or locating on endothelial surface, are intrinsically active and hyperadhesive because the functional A1 domain are continuously exposed [27,31]. Activated VWF and freshly released ULVWF can also mediate leukocyte recruitment to facilitate inflammatory endotheliopathy at the site of injury and elsewhere either directly or indirectly after binding platelets [122,123]. Consistent with this notion, neutrophil activation and the formation of neutrophil extracellular traps (NETs) have been found to be involved in thromboinflammatory response to COVID-19 [124–126]. VWF interacts with NETs to provide a scaffold for platelet/leukocyte adhesion thus promoting thrombus formation and inflammation [28,127], which also observed in patients with COVID-19 [24,128]. In addition, Ackermann et al [89] reported an unexpected new vessel growth within lungs of COVID-19 patients through a mechanism of intussusceptive angiogenesis, and speculated that it is because of endothelialitis and thrombosis in the lungs. Similarly, we have recently shown that VWF served as a coupling factor that tethered platelet-derived extracellular vesicles (EVs) to ECs, thus locally concentrating vascular endothelial growth factor (VEGF) for aberrant angiogenesis in patients with left ventricular assist device implantation [129]. We also found that hyperadhesive VWF released during acute traumatic brain injury mediated EVs to active ECs and platelets, thus responsible for consumptive coagulopathy and vascular leakage in the brain and the lung [31,32]. Increased circulating EVs, containing pro-coagulant, proinflammatory, and prothrombotic factors in their cargo, have been reported to be predictive biomarkers and likely to enhance immunothrombosis in patients with COVID-19 [130–136]. Hence, VWF tethered EVs (VWF⁺EVs) may also be involved in COVID-19-associated endotheliopathy and coagulopathy, and a promising diagnostic or prognostic marker.

A key determinant of VWF functional capacity is that larger VWF size is more active due to more monomeric subunits and higher sensitivity for shear forces [137,138]. ADAMTS13, mainly synthesized in hepatic stellate cells, is primarily responsible for specifically cleaving the ULVWF (>10,000 kDa; Tyr1605-Met1606 peptide bond within A2 domain) to smaller and less active multimers (<10,000 kDa), thus preventing the spontaneous intravascular platelet aggregation and resultant thromboembolism, as is seen in patients with thrombotic thrombocytopenic purpura (TTP), while maintaining the basic hemostatic activity of VWF [138,139]. Roh et al. [140] recently performed a case-control plasma proteomics study, and demonstrated that, of the 4996 protein analytes assessed, ADAMTS13 was the most significantly decreased in severe COVID-19, and displayed the strongest inverse association with myocardial injury. Abnormalities in plasma VWF multimeric pattern have been reported in patients with COVID-19. Several groups reported a relative decreased high molecular weight multimer (HMWM) of VWF in COVID-19 patients [55,68,141], which could be explained by an early increase in VWF proteolysis by ADAMTS13. This may also be attributable in part to the formation of ULVWF-platelet aggregates and the corresponding VWF and platelet consumption. However, thrombocytopenia is relatively rare in COVID-19 patients [4,16]. But other studies of severe COVID-19 have observed evidence of increased HMWM [76,81]. The differences likely due to the study cohort recruitment, time of sample collection, and the methodologies of VWF multimer distribution [141]. The exact dynamic changes of VWF multimeric pattern after COVID-19 still need further study. The majority of studies reported normal or mildly to moderately decreased ADAMTS13:Ac levels [51,62,70,72,80,87], and a strongly elevated VWF:Ag/ADAMTS13:Ac ratio in patients with COVID-19 when compared to healthy controls, especially in those with worse illness or in non-survivors [55,70,80]. We

confirmed that lower levels of ADAMTS13:Ac and higher VWF:Ag/ADAMTS13:Ac ratio and VWF:Rco were related to poor clinical outcomes. Several lines of evidence indicated that this is because massive increase of VWF with relative deficiency of ADAMTS13: 1) inflammatory cytokines and/or tissue hypoxia induce massively increased WPB exocytosis of VWF multimers by activating ECs [73,142–144]; 2) there is no alteration in ADAMTS13 gene expression after stimulation of liver cells with pro-inflammatory stimuli [145]; 3) there is no intracellular storage pool of ADAMTS13 [146]. The latter two suggest ADAMTS13 may not increase as rapidly after COVID-19 as VWF does. Other possible mechanisms contributing this imbalanced VWF-ADAMTS13 axis include: 1) inflammatory (including complement and NET products) [144,147] and oxidative [148,149] mediators enhance VWF self-association to increase VWF reactivity, make VWF resistant to cleavage, and reduce ADAMTS13 activity in cleaving VWF; 2) reduced ADAMTS13 synthesis because of COVID-19-induced pathologies of the liver [146,150,151]; 3) Considering high-density lipoprotein (HDL) prevents VWF self-association, while low-density lipoprotein (LDL) has the opposite effect [26]. HDL reduction and LDL elevation observed in patients with COVID-19 may also contribute to the imbalanced VWF-ADAMTS13 axis [62,152].

Although several case reports showed SARS-CoV-2 infection trigger acute TTP [153–155], and therapeutic plasma exchange, a mainstay treatment for TTP, has shown to reduce immunothrombosis while improve respiratory parameters and clinical outcomes in critically ill patients with COVID-19 [156–158]. CAC do not resemble a classic TTP since there is lack of severe ADAMTS13 deficiency (activity levels <10%), major thrombocytopenia, or hemolytic anemia [22,54,64,68,70,80,81]. However, the imbalanced VWF-ADAMTS13 axis combined with clinical and pathologic findings of widespread microvascular thrombi in multi-organs may suggest a secondary TMA-like phenomenon [62], which can also be seen in other forms of TMA (drug, cancer, or hematopoietic stem cell transplant induced TMA [159]) and thrombotic disorders (e.g., severe sepsis, malaria, trauma, and preeclampsia) [29–39]. Here, we speculate the mechanisms that link VWF-ADAMTS13 axis, endotheliopathy, and CAC: SARS-CoV-2 direct invasion and/or indirect pathophysiological conditions induce endotheliopathy and subsequent overwhelming ULVWF release. Multiple mechanisms, including pro-inflammatory and oxidative mediator milieu, reduced hepatic ADAMTS13 synthesis due to liver injury, or imbalanced HDL/LDL levels, induce reduced cleavage of ADAMTS13 and dysregulation of VWF proteolysis. This imbalanced VWF-ADAMTS13 axis ultimately trigger immunothrombosis and lead to CAC, first localized to lung, then eventually spreading systematically and leading to multi-organ damage. Further vigorous experimental and prospective clinical studies are warranted to elucidate the exact role of VWF-ADAMTS13 axis in the pathophysiological process of COVID-19 as well as the mechanisms by which it becomes imbalanced. Also, in addition to aforementioned ultima ratio therapy of plasma exchange (remove VWF and replenish ADAMTS13) [158], strategies that specifically balance VWF-ADAMTS13 axis may have therapeutic effects on COVID-19. A recent study from a cross-sectional cohort of 36 severe COVID-19 patients indicated that incubation of patient plasma samples with recombinant ADAMTS13 resulted in a time- and concentration-dependent reduction in abnormally high VWF activity and VWF multimer size, suggesting a potential therapeutic role in treating COVID-19 [160]. Caplacizumab is a humanized immunoglobulin specifically targeting the VWF A1 domain, blocking its interaction with platelet receptor GPIIb and thereby preventing platelet aggregation. It is the first nanobody drug approved by the US Food and Drug Administration (FDA) to treat adult acquired TTP, which is caused by the development of anti-ADAMTS13 autoantibodies and subsequent accumulation ULVWF [161,162]. We thus propose to consider caplacizumab as a new treatment option. In this regard, anti-VWF A1 aptamers, such as ARC1779 [163], TAGX-0004 [164], and BT200 [165], may also be novel therapies. Similarly, we recently demonstrated that recombinant VWF

A2 domain prevented traumatic brain injury-induced coagulopathy by selectively blocking the exposed A1 domain of the hyperadhesive VWF [31]. We also found that A2 specifically bound activated VWF in the plasma of a TTP patient [31]. In addition, *N*-acetylcysteine (NAC) is a FDA-approved pleiotropic drug with anti-oxidant and anti-inflammatory mechanisms, primarily for the treatment of pulmonary diseases. NAC can also reduce VWF multimers and inhibit VWF-dependent platelet aggregation and collagen binding [166]. Many studies have shown that NAC reduced disease severity in the treatment of COVID-19 patients [167–169]. Of interest, several clinical trials using NAC in COVID-19 have been registered and implemented (e.g., NCT04374461, NCT04419025, and NCT05074121), and these results will clarify its safety and efficacy [169].

4.3. Limitation

First, most of the included studies are observational retrospective with small sample size, and the study results are high heterogeneous. Second, there is no standardized method to measure VWF-related variables. These were either in-house assays or from different commercial manufacturers, and thus might lead to different values. Third, the time of sample collection varied and could attribute to different outcome measures. Fourth, due to the lack of individual patient data, multivariable regression analyses could not be performed to adjust for potential confounding influences (e.g., blood type, age, sex, body mass index, diabetes, hypertension, and medication usage) [82,170]. Despite these limitations, this study represents a large systematic reviews and meta-analysis to investigate the association between changes in VWF-related variables and clinical outcomes in the COVID-19 population.

5. Conclusion

Increased plasma levels of VWF:Ag, VWF:Rco, VWF:Ag/ADAMTS13:Ac ratio, and FVIII, and decreased ADAMTS13:Ac are associated with unfavorable outcomes of patients with COVID-19. However, there are currently insufficient data available to recommend VWF-related variables as routine clinical assessments.

Abbreviations

ACE2	angiotensin-converting enzyme 2
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADAMTS13 Ac:	ADAMTS13 activity
ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
CAC	COVID-19-associated coagulopathy
CI	confidence interval
DIC	diffuse intravascular coagulopathy
EC	endothelial cell
EV	extracellular vesicles
FDA	Food and Drug Administration
FVIII	factor VIII
GP	glycoprotein
HDL	high-density lipoprotein
ICAM-1	intercellular adhesion molecule-1
ICU	intensive care unit
IL	interleukin
LDL	low-density lipoprotein
NAC	<i>N</i> -acetylcysteine
NETs	neutrophil extracellular traps
NOS	Newcastle-Ottawa Scale
PT	prothrombin time
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMD	standardized mean difference
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
VEGF	vascular endothelial growth factor
VWF	von Willebrand factor
VWF:Ag	VWF antigen
VWF:Rco	VWF ristocetin cofactor
VWFpp	VWF propeptide
ULVWF	ultra-large VWF
WPB	weibel-palade bodie

Ethics approval and consent to participate

Not applicable.

Consent for publication.

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

XX and YF designed the study. YJ, XZ, and XB performed the literature search, assessed the quality of the literature, and extracted the data independently. YF and LL did the statistical analysis. XX, YF, and LL interpreted the results and drafted the manuscript. LJ and XX reviewed and revised the manuscript and supervised the study. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no competing interest in this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2022.08.017>.

References

- [1] R.W. Peeling, D.L. Heymann, Y.Y. Teo, P.J. Garcia, Diagnostics for COVID-19: moving from pandemic response to control, *Lancet* 399 (2021) 757–768.
- [2] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet* 395 (2020) 497–506.
- [3] A. Gupta, M.V. Madhavan, K. Sehgal, N. Nair, S. Mahajan, T.S. Sehrawat, et al., Extrapulmonary manifestations of COVID-19, *Nat. Med.* 26 (2020) 1017–1032.

- [4] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, *J. ThrombosisHaemostasis* 18 (2020) 844–847.
- [5] F.A. Klok, M. Kruij, N.J.M. van der Meer, M.S. Arbois, D. Gommers, K.M. Kant, et al., Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis, *Thromb. Res.* 191 (2020) 148–150.
- [6] J. Helms, C. Tacquard, F. Severac, I. Leonard-Lorant, M. Ohana, X. Delabranche, et al., High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study, *Intensive Care Med.* 46 (2020) 1089–1098.
- [7] W.J. Jenner, R. Kanji, S. Mirsadraee, Y.X. Gue, S. Price, S. Prasad, et al., Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review, *J. Thromb. Thrombolysis* 51 (2021) 595–607.
- [8] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, et al., Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, *Thromb. Res.* 191 (2020) 9–14.
- [9] I. Katsoularis, O. Fonseca-Rodriguez, P. Farrington, K. Lindmark, A.M. Fors Connolly, Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study, *Lancet* 398 (2021) 599–607.
- [10] D. Modin, B. Claggett, C. Sindet-Pedersen, M.C.H. Lassen, K.G. Skaarup, J.U. S. Jensen, et al., Acute COVID-19 and the incidence of ischemic stroke and acute myocardial infarction, *Circulation* 142 (2020) 2080–2082.
- [11] S. Satturwar, M. Fowkes, C. Farver, A.M. Wilson, A. Echer, I. Girolami, et al., Postmortem findings associated with SARS-CoV-2: systematic review and meta-analysis, *Am. J. Surg. Pathol.* 45 (2021) 587–603.
- [12] A.V. Rapkiewicz, X. Mai, S.E. Carsons, S. Pitaluga, D.E. Kleiner, J.S. Berger, et al., Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series, *EClinicalMedicine* 24 (2020), 100434.
- [13] S.E. Fox, A. Akmatbekov, J.L. Harbert, G. Li, J. Quincy Brown, R.S. Vander Heide, Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans, *Lancet Respir. Med.* 8 (2020) 681–686.
- [14] D. Pellegrini, R. Kawakami, G. Guagliumi, A. Sakamoto, K. Kawai, A. Gianatti, et al., Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study, *Circulation* 143 (2021) 1031–1042.
- [15] D. Elieh Ali Komi, Y. Rahimi, R. Ashgari, R. Jafari, J. Rasouli, M. Mohebalizadeh, et al., Investigation of the molecular mechanism of coagulopathy in severe and critical patients with COVID-19, *Front. Immunol.* 12 (2021) 762782.
- [16] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, et al., ISTH interim guidance on recognition and management of coagulopathy in COVID-19, *J. ThrombosisHaemostasis* 18 (2020) 1023–1026.
- [17] M. Levi, M. Scully, How I treat disseminated intravascular coagulation, *Blood* 131 (2018) 845–854.
- [18] Y. Cao, C. Geng, Y. Li, Y. Zhang, In situ pulmonary artery thrombosis: a previously overlooked disease, *Front. Pharmacol.* 12 (2021), 671589.
- [19] E. Gavriilaki, R.A. Brodsky, Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily, *Br. J. Haematol.* 189 (2020) e227–e230.
- [20] M. Levi, J. Thachil, Coronavirus disease 2019 coagulopathy: disseminated intravascular coagulation and thrombotic microangiopathy—either, neither, or both, *Semin. Thromb. Hemost.* 46 (2020) 781–784.
- [21] T. Iba, J.H. Levy, J.M. Connors, T.E. Warkentin, J. Thachil, M. Levi, The unique characteristics of COVID-19 coagulopathy, *Crit. Care* 24 (2020) 360.
- [22] M. Scully, S. Cataland, P. Coppo, J. de la Rubia, K.D. Friedman, J. Kremer Hovinga, et al., Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies, *J. Thromb. Haemostasis* 15 (2017) 312–322.
- [23] P. Libby, T. Luscher, COVID-19 is, in the end, an endothelial disease, *Eur. Heart J.* 41 (2020) 3038–3044.
- [24] A. Dupont, A. Rauch, S. Staessens, M. Moussa, M. Rosa, D. Corseaux, et al., Vascular endothelial damage in the pathogenesis of organ injury in severe COVID-19, *Arterioscler. Thromb. Vasc. Biol.* 41 (2021) 1760–1773.
- [25] A. Bonaventura, A. Vecchie, L. Dagna, K. Martinod, D.L. Dixon, B.W. Van Tassel, et al., Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19, *Nat. Rev. Immunol.* 21 (2021) 319–329.
- [26] J. Chen, D.W. Chung, Inflammation, von Willebrand factor, and ADAMTS13, *Blood* 132 (2018) 141–147.
- [27] F. Denorme, K. Vanhoorelbeke, S.F. De Meyer, von Willebrand factor and platelet glycoprotein Ib: a thromboinflammatory axis in stroke, *Front. Immunol.* 10 (2019) 2884.
- [28] J. Yang, Z. Wu, Q. Long, J. Huang, T. Hong, W. Liu, et al., Insights into immunothrombosis: the interplay among neutrophil extracellular trap, von Willebrand factor, and ADAMTS13, *Front. Immunol.* 11 (2020), 610696.
- [29] T.A. MacArthur, J. Goswami, L. Moon Tasson, A. Tischer, K.R. Bailey, G. M. Spears, et al., Quantification of von Willebrand factor and ADAMTS-13 after traumatic injury: a pilot study, *Trauma Surg. Acute Care Open* 6 (2021), e000703.
- [30] W.E. Plautz, S.H. Haldeman, M.R. Dyer, J.L. Sperry, F.X. Guyette, P.A. Loughran, et al., Reduced cleavage of von Willebrand factor by ADAMTS13 is associated with microangiopathic acute kidney injury following trauma, *Blood Coagulat. Fibrinolysis* 33 (2022) 14–24.
- [31] X. Xu, C. Wang, Y. Wu, K. Houck, T. Hilton, A. Zhou, et al., Conformation-dependent blockage of activated VWF improves outcomes of traumatic brain injury in mice, *Blood* 137 (2021) 544–555.
- [32] Y. Wu, W. Liu, Y. Zhou, T. Hilton, Z. Zhao, W. Liu, et al., von Willebrand factor enhances microvesicle-induced vascular leakage and coagulopathy in mice with traumatic brain injury, *Blood* 132 (2018) 1075–1084.
- [33] M. Peetermans, S. Meyers, L. Liesenborghs, K. Vanhoorelbeke, S.F. De Meyer, C. Vandenberghe, et al., Von Willebrand factor and ADAMTS13 impact on the outcome of Staphylococcus aureus sepsis, *J. Thromb. Haemostasis* 18 (2020) 722–731.
- [34] M. Levi, M. Scully, M. Singer, The role of ADAMTS-13 in the coagulopathy of sepsis, *J. Thromb. Haemostasis* 16 (2018) 646–651.
- [35] M. Schwameis, C. Schorgenhofer, A. Assinger, M.M. Steiner, B. Jilma, VWF excess and ADAMTS13 deficiency: a unifying pathomechanism linking inflammation to thrombosis in DIC, malaria, and TTP, *Thromb. Haemost.* 113 (2015) 708–718.
- [36] Y. Chen, P. Huang, C. Han, J. Li, L. Liu, Z. Zhao, et al., Association of placenta-derived extracellular vesicles with pre-eclampsia and associated hypercoagulability: a clinical observational study, *BJOG* 128 (2021) 1037–1046.
- [37] A. Stepanian, M. Cohen-Moatti, T. Sanglier, P. Legendre, N. Ameziane, V. Tsatsaris, et al., Von Willebrand factor and ADAMTS13: a candidate couple for preeclampsia pathophysiology, *Arterioscler. Thromb. Vasc. Biol.* 31 (2011) 1703–1709.
- [38] M.A. Sonneveld, M.P. de Maat, M.L. Portegies, M. Kavousi, A. Hofman, P. L. Turecek, et al., Low ADAMTS13 activity is associated with an increased risk of ischemic stroke, *Blood* 126 (2015) 2739–2746.
- [39] H.M. Andersson, B. Siegerink, B.M. Luken, J.T. Crawley, A. Algra, D.A. Lane, et al., High VWF, low ADAMTS13, and oral contraceptives increase the risk of ischemic stroke and myocardial infarction in young women, *Blood* 119 (2012) 1555–1560.
- [40] E.J. Favaloro, B.M. Henry, G. Lippi, Increased VWF and decreased ADAMTS-13 in COVID-19: creating a milieu for (micro)thrombosis, *Semin. Thromb. Hemost.* 47 (2021) 400–418.
- [41] R. Seth, T.A.J. McKinnon, X.F. Zhang, Contribution of the von Willebrand factor/ADAMTS13 imbalance to COVID-19 coagulopathy, *Am. J. Physiol. Heart Circ. Physiol.* 322 (2022) H87–H93.
- [42] Andrianto, M.J. Al-Farabi, R.A. Nugraha, B.A. Marsudi, Y. Azmi, Biomarkers of endothelial dysfunction and outcomes in coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis, *Microvasc. Res.* 138 (2021), 104224.
- [43] A. Wibowo, R. Pranata, M.A. Lim, M.R. Akbar, J.W. Martha, Endotheliopathy marked by high von Willebrand factor (vWF) antigen in COVID-19 is associated with poor outcome: a systematic review and meta-analysis, in: *Int. J. Infect. Dis.*, 2021.
- [44] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *BMJ* 339 (2009), b2535.
- [45] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, *BMC Med. Res. Methodol.* 14 (2014) 135.
- [46] J. Shi, D. Luo, X. Wan, Y. Liu, J. Liu, Z. Bian, et al., Detecting the skewness of data from the sample size and the five-number summary, 2020.
- [47] A.V. Margulis, M. Pladevall, N. Riera-Guardia, C. Varas-Lorenzo, L. Hazell, N. D. Berkman, et al., Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank, *Clin Epidemiol.* 6 (2014) 359–368.
- [48] T. Wang, X. Wang, K. Yang, J. Zhang, J. Luo, P. Gao, et al., Endovascular treatment for symptomatic intracranial artery stenosis: protocol for a systematic review and network meta-analysis, *BMJ Open* 8 (2018), e022359.
- [49] W. Bauer, N. Galtung, N. Neuwinger, L. Kaufner, E. Langer, R. Somasundaram, et al., A matter of caution: coagulation parameters in COVID-19 do not differ from patients with ruled-out SARS-CoV-2 infection in the emergency department, *TH Open* 5 (2021) e43–e55.
- [50] M. Bazzan, B. Montaruli, S. Sciascia, D. Cosseddu, C. Norbiato, D. Roccatello, Low ADAMTS 13 plasma levels are predictors of mortality in COVID-19 patients, *Intern. Emerg. Med.* 15 (2020) 861–863.
- [51] A. Blasi, F.A. von Meijenfeldt, J. Adelmeyer, A. Calvo, C. Ibanez, J. Perdomo, et al., In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation, *J. Thromb. Haemostasis* 18 (2020) 2646–2653.
- [52] M. Cugno, P.L. Meroni, R. Gualtierotti, S. Griffini, E. Grovetti, A. Torri, et al., Complement activation and endothelial perturbation parallel COVID-19 severity and activity, *J. Autoimmun.* 116 (2021), 102560.
- [53] R. De Jongh, M. Ninivaggi, D. Mesotten, C. Bai, B. Marcus, D. Huskens, et al., Vascular activation is a strong predictor of mortality in coronavirus disease 2019 patients on the ICU, *Blood Coagul. Fibrinolysis* 32 (2021) 290–293.
- [54] M. Delrue, V. Siguret, M. Neuwirth, B. Joly, N. Beranger, D. Sene, et al., von Willebrand factor/ADAMTS13 axis and venous thromboembolism in moderate-to-severe COVID-19 patients, *Br. J. Haematol.* 192 (2021) 1097–1100.
- [55] A.A.N. Doevelaar, M. Bachmann, B. Holzer, F.S. Seibert, B.J. Rohn, F. Bauer, et al., von Willebrand factor multimer formation contributes to immunothrombosis in coronavirus disease 2019, *Crit. Care Med.* 49 (2021) e512–e520.
- [56] A. Dushianthan, N. Abdul, J. Dmochowski, I. James, L. Heesom, J. Westwood, et al., Predictive role of haematological determinants on outcomes of critically ill COVID-19 patients admitted to intensive care unit, *Cureus* 13 (2021), e16764.
- [57] B.E. Fan, K. Ramanathan, C.L.L. Sum, D. Christopher, S.S.W. Chan, G.H. Lim, et al., Global haemostatic tests demonstrate the absence of parameters of hypercoagulability in non-hypoxic mild COVID-19 patients: a prospective matched study, *J. Thromb. Thrombolysis* 53 (2021) 646–662.
- [58] S. Fernandez, A.B. Moreno-Castano, M. Palomo, J. Martinez-Sanchez, S. Torramade-Moix, A. Tellez, et al., Distinctive biomarker features in the endotheliopathy of COVID-19 and septic syndromes, *Shock* 57 (2022) 95–105.

- [59] I.M.B. Francischetti, K. Toomer, Y. Zhang, J. Jani, Z. Siddiqui, D.J. Brotman, et al., Upregulation of pulmonary tissue factor, loss of thrombomodulin and immunothrombosis in SARS-CoV-2 infection, *EclinicalMedicine* 39 (2021), 101069.
- [60] G. Goshua, A.B. Pine, M.L. Meizlish, C.H. Chang, H. Zhang, P. Bahel, et al., Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study, *Lancet Haematol.* 7 (2020) e575–e582.
- [61] T.A. Helin, M. Lemponen, T. Lahtiharju, M. Koskinen, R. Lassila, L. Joutsikorhonen, Anaemia and enhancement of coagulation are associated with severe COVID-19 infection, *Scand. J. Clin. Lab. Invest.* 81 (2021) 653–660.
- [62] B.M. Henry, S.W. Benoit, M.H.S. de Oliveira, G. Lippi, E.J. Favaloro, J.L. Benoit, ADAMTS13 activity to von Willebrand factor antigen ratio predicts acute kidney injury in patients with COVID-19: evidence of SARS-CoV-2 induced secondary thrombotic microangiopathy, *Int. J. Lab. Hematol.* 43 (Suppl 1) (2021) 129–136.
- [63] C. Herr, S. Mang, B. Mozafari, K. Guenther, T. Speer, M. Seibert, et al., Distinct patterns of blood cytokines beyond a cytokine storm predict mortality in COVID-19, *J. Inflamm. Res.* 14 (2021) 4651–4667.
- [64] B.S. Joly, M. Darmon, C. Dekimpe, T. Dupont, G. Dumas, E. Yvin, et al., Imbalance of von Willebrand factor and ADAMTS13 axis is rather a biomarker of strong inflammation and endothelial damage than a cause of thrombotic process in critically ill COVID-19 patients, *J.Thromb.Haemostasis* 19 (2021) 2193–2198.
- [65] D. Jothimani, E. Kailasam, B. Nallathambi, S. Danielraj, H. Ramachandran, K. Narayanan, et al., COVID 19: elevated von Willebrand factor at hospital admission predicts clinical outcomes, *J. Assoc. Physicians India* 69 (2021) 16–21.
- [66] Y. Lichter, T. Badelbayov, I. Shalev, R. Schwartz, Y. Szekely, D. Benisty, et al., Low FXIII activity levels in intensive care unit hospitalized COVID-19 patients, *Thromb. J.* 19 (2021) 79.
- [67] S. Lopez-Castaneda, N. Garcia-Larragoiti, A. Cano-Mendez, K. Blancas-Ayala, G. Damian-Vazquez, A.I. Perez-Medina, et al., Inflammatory and prothrombotic biomarkers associated with the severity of COVID-19 infection, *Clin.Appl. Thromb.Hemost.* 27 (2021), 1076029621999099.
- [68] I. Mancini, L. Baronciani, A. Artoni, P. Colpani, M. Biganzoli, G. Cozzi, et al., The ADAMTS13-von Willebrand factor axis in COVID-19 patients, *J.Thromb. Haemostasis* 19 (2021) 513–521.
- [69] M. Marchetti, P. Gomez-Rosas, E. Sanga, S. Gamba, C. Verzeroli, L. Russo, et al., Endothelium activation markers in severe hospitalized COVID-19 patients: role in mortality risk prediction, *TH Open* 5 (2021) e253–e263.
- [70] A. Marco, P. Marco, Von Willebrand factor and ADAMTS13 activity as clinical severity markers in patients with COVID-19, *J. Thromb. Thrombolysis* 52 (2021) 497–503.
- [71] R.M. Martin-Rojas, G. Perez-Rus, V.E. Delgado-Pinos, A. Domingo-Gonzalez, I. Regalado-Artamendi, N. Alba-Urdiales, et al., COVID-19 coagulopathy: an in-depth analysis of the coagulation system, *Eur. J. Haematol.* 105 (2020) 741–750.
- [72] R.M. Martin-Rojas, M. Chasco-Ganuza, S. Casanova-Prieto, V.E. Delgado-Pinos, G. Perez-Rus, P. Duque-Gonzalez, et al., A mild deficiency of ADAMTS13 is associated with severity in COVID-19: comparison of the coagulation profile in critically and noncritically ill patients, *Blood Coagul.Fibrinolysis* 32 (2021) 458–467.
- [73] V. Montiel, I. Lobysheva, L. Gerard, M. Vermeersch, D. Perez-Morga, T. Castelein, et al., Oxidative stress-induced endothelial dysfunction and decreased vascular nitric oxide in COVID-19 patients, *EBioMedicine* 77 (2022), 103893.
- [74] C. Nougier, R. Benoit, M. Simon, H. Desmurs-Clavel, G. Marcotte, L. Argaud, et al., Hypofibrinolytic state and high thrombin generation may play a major role in SARS-CoV2 associated thrombosis, *J.Thromb.Haemostasis* 18 (2020) 2215–2219.
- [75] T. Pascreau, S. Zia-Chahabi, B. Zuber, C. Tcherakian, E. Farfour, M. Vasse, ADAMTS 13 deficiency is associated with abnormal distribution of von Willebrand factor multimers in patients with COVID-19, *Thromb. Res.* 204 (2021) 138–140.
- [76] A. Philippe, R. Chocron, N. Gendron, O. Bory, A. Beauvais, N. Peron, et al., Circulating Von Willebrand factor and high molecular weight multimers as markers of endothelial injury predict COVID-19 in-hospital mortality, *Angiogenesis* 24 (2021) 505–517.
- [77] A. Philippe, N. Gendron, O. Bory, A. Beauvais, T. Mirault, B. Planquette, et al., Von Willebrand factor collagen-binding capacity predicts in-hospital mortality in COVID-19 patients: insight from VWF/ADAMTS13 ratio imbalance, *Angiogenesis* 24 (2021) 407–411.
- [78] A. Rauch, J. Labreuche, F. Lassalle, J. Goutay, M. Caplan, L. Charbonnier, et al., Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19, *J.Thromb.Haemostasis* 18 (2020) 2942–2953.
- [79] M. Rodriguez Rodriguez, N. Castro Quismondo, D. Zafra Torres, D. Gil Alos, R. Ayala, J. Martinez-Lopez, Increased von Willebrand factor antigen and low ADAMTS13 activity are related to poor prognosis in COVID-19 patients, *Int. J. Lab. Hematol.* 43 (2021) O152–O155.
- [80] G. Sinkovits, M. Reti, V. Muller, Z. Ivanyi, J. Gal, L. Gopcsa, et al., Associations between the von Willebrand factor-ADAMTS13 axis, complement activation, and COVID-19 severity and mortality, *Thromb. Haemost.* 122 (2022) 240–256.
- [81] J.M. Sweeney, M. Barouqa, G.J. Krause, J.D. Gonzalez-Lugo, S. Rahman, M.R. Gil, Low ADAMTS13 activity correlates with increased mortality in COVID-19 patients, *TH Open* 5 (2021) e89–e103.
- [82] K. Thangaraju, U. Katneni, I.J. Akpan, K. Tanaka, T. Thomas, S. Setua, et al., The impact of age and BMI on the VWF/ADAMTS13 axis and simultaneous thrombin and plasmin generation in hospitalized COVID-19 patients, *Front.Med.* 8 (2021), 817305.
- [83] V.V. Thomas, S.E. Kumar, V. Alexander, A. Nadaraj, B. Vijayalekshmi, S. Prabhu, et al., Plasma von Willebrand factor levels predict survival in COVID-19 patients across the entire Spectrum of disease severity, in: *Indian J.Hematol.Blood Transfus.*, 2021, pp. 1–8.
- [84] G. Tiscia, G. Favuzzi, A. De Laurenzo, F. Cappucci, L. Fischetti, D. Colaizzo, et al., The prognostic value of ADAMTS-13 and von Willebrand factor in COVID-19 patients: prospective evaluation by care setting, *Diagnostics* 11 (2021).
- [85] J. Torres-Ruiz, A. Perez-Fragoso, J.L. Maravillas-Montero, L. Llorente, N.R. Mejia-Dominguez, J.C. Paez-Franco, et al., Redefining COVID-19 severity and prognosis: the role of clinical and immunobiotypes, *Front. Immunol.* 12 (2021), 689966.
- [86] A.G. Vassiliou, C. Keskinidou, E. Jahaj, P. Gallos, I. Dimopoulou, A. Kotanidou, et al., ICU admission levels of endothelial biomarkers as predictors of mortality in critically ill COVID-19 patients, *Cells* 10 (2021).
- [87] F.A. von Meijenfeldt, S. Havervall, J. Adelmeijer, A. Lundstrom, A.S. Rudberg, M. Magnusson, et al., Prothrombotic changes in patients with COVID-19 are associated with disease severity and mortality, *Res.Pract.Thromb.Haemost.* 5 (2021) 132–141.
- [88] D. Wichmann, J.P. Sperhake, M. Lutgehetmann, S. Steurer, C. Edler, A. Heinemann, et al., Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study, *Ann. Intern. Med.* 173 (2020) 268–277.
- [89] M. Ackermann, S.E. Verleden, M. Kuehnel, A. Haverich, T. Welte, F. Laenger, et al., Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19, *N. Engl. J. Med.* 383 (2020) 120–128.
- [90] T. Won, M.K. Wood, D.M. Hughes, M.V. Talor, Z. Ma, J. Schneider, et al., Endothelial thrombomodulin downregulation caused by hypoxia contributes to severe infiltration and coagulopathy in COVID-19 patient lungs, *EBioMedicine* 75 (2022), 103812.
- [91] M. Ranucci, A. Ballotta, U. Di Dedda, E. Baryshnikova, M. Dei Poli, M. Resta, et al., The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome, *J.Thromb.Haemostasis* 18 (2020) 1747–1751.
- [92] R. Cacciola, E. Gentilini Cacciola, V. Vecchio, E. Cacciola, Cellular and molecular mechanisms in COVID-19 coagulopathy: role of inflammation and endotheliopathy, *J. Thromb. Thrombolysis* 53 (2021) 282–290.
- [93] R.J. Jose, A. Manuel, COVID-19 cytokine storm: the interplay between inflammation and coagulation, *Lancet Respir. Med.* 8 (2020) e46–e47.
- [94] F. Ciceri, L. Beretta, A.M. Scandroglio, S. Colombo, G. Landoni, A. Ruggeri, et al., Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis, *Crit.CareResusc.* 22 (2020) 95–97.
- [95] I. Hamming, W. Timens, M.L. Bulthuis, A.T. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, *J. Pathol.* 203 (2004) 631–637.
- [96] V. Monteil, H. Kwon, P. Prado, A. Hagelkruys, R.A. Wimmer, M. Stahl, et al., Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2, *Cell* 181 (905–13) (2020), e7.
- [97] I.R. McCracken, G. Saginc, L. He, A. Huseynov, A. Daniels, S. Fletcher, et al., Lack of evidence of angiotensin-converting enzyme 2 expression and replicative infection by SARS-CoV-2 in human endothelial cells, *Circulation* 143 (2021) 865–868.
- [98] S. Deinhardt-Emmer, S. Bottcher, C. Haring, L. Giebeler, A. Henke, R. Zell, et al., SARS-CoV-2 causes severe epithelial inflammation and barrier dysfunction, *J. Virol.* 95 (2021) e00110–e00121.
- [99] J. Nascimento Conde, W.R. Schutt, E.E. Gorbunova, E.R. Mackow, Recombinant ACE2 expression is required for SARS-CoV-2 to infect primary human endothelial cells and induce inflammatory and procoagulative responses, *mBio* 11 (2020).
- [100] Z. Ma, K.Y. Yang, Y. Huang, K.O. Lui, Endothelial contribution to COVID-19: an update on mechanisms and therapeutic implications, *J. Mol. Cell. Cardiol.* 164 (2021) 69–82.
- [101] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, *Lancet* 395 (2020) 507–513.
- [102] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area, *JAMA* 323 (2020) 2052–2059.
- [103] E.J. Williamson, A.J. Walker, K. Bhaskaran, S. Bacon, C. Bates, C.E. Morton, et al., Factors associated with COVID-19-related death using OpenSAFELY, *Nature* 584 (2020) 430–436.
- [104] J. Yin, S. Wang, Y. Liu, J. Chen, D. Li, T. Xu, Coronary microvascular dysfunction pathophysiology in COVID-19, *Microcirculation* 28 (2021), e12718.
- [105] R.M. Inciardi, L. Lupi, G. Zacccone, L. Italia, M. Raffo, D. Tomasoni, et al., Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19), *JAMA Cardiol.* 5 (2020) 819–824.
- [106] D.A. Gorog, R.F. Storey, P.A. Gurbel, U.S. Tantry, J.S. Berger, M.Y. Chan, et al., Current and novel biomarkers of thrombotic risk in COVID-19: a consensus statement from the international COVID-19 thrombosis biomarkers colloquium, *Nat. Rev. Cardiol.* 19 (2022) 475–495.
- [107] S. Lampsas, P. Tsaplaris, P. Pantelidis, E. Oikonomou, G. Marinos, G. Charalambous, et al., The role of endothelial related circulating biomarkers in COVID-19. A systematic review and meta-analysis, *Curr. Med. Chem.* 29 (2021) 3790–3805.
- [108] S.L. Haberichter, von Willebrand factor propeptide: biology and clinical utility, *Blood* 126 (2015) 1753–1761.
- [109] P.-J. Lenting, O.D. Christophe, C.V. Denis, von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends, *Blood* 125 (2015) 2019–2028.
- [110] Y.F. Zhou, E.T. Eng, J. Zhu, C. Lu, T. Walz, T.A. Springer, Sequence and structure relationships within von Willebrand factor, *Blood* 120 (2012) 449–458.

- [111] L.A. Sporn, V.J. Marder, D.D. Wagner, Inducible secretion of large, biologically potent von Willebrand factor multimers, *Cell* 46 (1986) 185–190.
- [112] A.S. Babkina, I.V. Ostrova, M.Y. Yadgarov, A.N. Kuzovlev, A.V. Grechko, A. V. Volkov, et al., The role of von Willebrand factor in the pathogenesis of pulmonary vascular thrombosis in COVID-19, *Viruses* 14 (2022).
- [113] F. Taus, G. Salvagno, S. Cane, C. Fava, F. Mazzaferri, E. Carrara, et al., Platelets promote thromboinflammation in SARS-CoV-2 pneumonia, *Arterioscler. Thromb. Vasc. Biol.* 40 (2020) 2975–2989.
- [114] S.E. Ward, G.F. Curley, M. Lavin, H. Fogarty, E. Karampini, N.L. McEvoy, et al., Von Willebrand factor propeptide in severe coronavirus disease 2019 (COVID-19): evidence of acute and sustained endothelial cell activation, *Br. J. Haematol.* 192 (2021) 714–719.
- [115] H. Fogarty, L. Townsend, H. Morrin, A. Ahmad, C. Comerford, E. Karampini, et al., Persistent endotheliopathy in the pathogenesis of long COVID syndrome, *J. Thromb. Haemostasis* 19 (2021) 2546–2553.
- [116] M.S. Alkodaymi, O.A. Omrani, N.A. Fawzy, B.A. Shaar, R. Almamlouk, M. Riaz, et al., Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis, in: *Clin. Microbiol. Infect.*, 2022.
- [117] F.A. von Meijenfheldt, S. Havervall, J. Adelmeijer, A. Lundstrom, M. Magnusson, N. Mackman, et al., Sustained prothrombotic changes in COVID-19 patients 4 months after hospital discharge, *Blood Adv.* 5 (2021) 756–759.
- [118] K. Yamamoto, V. de Waard, C. Fearn, D.J. Loskutoff, Tissue distribution and regulation of murine von Willebrand factor gene expression in vivo, *Blood* 92 (1998) 2791–2801.
- [119] K.L. Wion, D. Kelly, J.A. Summerfield, E.G. Tuddenham, R.M. Lawn, Distribution of factor VIII mRNA and antigen in human liver and other tissues, *Nature* 317 (1985) 726–729.
- [120] A. Mojzisch, M.A. Brehm, The manifold cellular functions of von Willebrand factor, *Cells* 10 (2021).
- [121] M. Shahidi, Thrombosis and von Willebrand factor, *Adv. Exp. Med. Biol.* 906 (2017) 285–306.
- [122] B. Petri, A. Broermann, H. Li, A.G. Khandoga, A. Zarbock, F. Krombach, et al., von Willebrand factor promotes leukocyte extravasation, *Blood* 116 (2010) 4712–4719.
- [123] F. Denorme, K. Martinod, A. Vandenbulcke, C.V. Denis, P.J. Lenting, H. Deckmyn, et al., The von Willebrand factor A1 domain mediates thromboinflammation, aggravating ischemic stroke outcome in mice, *Haematologica* 106 (2021) 819–828.
- [124] N. Kinnare, J.S. Hook, P.A. Patel, N.L. Monson, J.G. Moreland, Neutrophil extracellular trap formation potential correlates with lung disease severity in COVID-19 patients, *Inflammation* 45 (2021) 800–811.
- [125] H. Ng, S. Havervall, A. Rosell, K. Aguilera, K. Parv, F.A. von Meijenfheldt, et al., Circulating markers of neutrophil extracellular traps are of prognostic value in patients with COVID-19, *Arterioscler. Thromb. Vasc. Biol.* 41 (2021) 988–994.
- [126] C. Radermecker, N. Detrembleur, J. Guiot, E. Cavalier, M. Henket, C. d'Emal, et al., Neutrophil extracellular traps infiltrate the lung airway, interstitial, and vascular compartments in severe COVID-19, *J. Exp. Med.* 217 (2020).
- [127] M. Ackermann, H.J. Anders, R. Bilyk, G.L. Bowlin, C. Daniel, R. De Lorenzo, et al., Patients with COVID-19: in the dark-NETs of neutrophils, *Cell Death Differ.* 28 (2021) 3125–3139.
- [128] E. Toth, L. Beinrohr, I. Gubucz, L. Szabo, K. Tenekedjiev, N. Nikolova, et al., Fibrin to von Willebrand factor ratio in arterial thrombi is associated with plasma levels of inflammatory biomarkers and local abundance of extracellular DNA, *Thromb. Res.* 209 (2022) 8–15.
- [129] M. Yang, K.L. Houck, X. Dong, M. Hernandez, Y. Wang, S.S. Nathan, et al., Hyperadhesive von Willebrand factor promotes extracellular vesicle-induced angiogenesis: implication for LVAD-induced bleeding, *JACC BasicTransl.Sci.* 7 (2022) 247–261.
- [130] E. Campello, C.M. Radu, C. Simion, L. Spiezia, C. Bulato, S. Gavasso, et al., Longitudinal trend of plasma concentrations of extracellular vesicles in patients hospitalized for COVID-19, *Front. Cell Dev. Biol.* 9 (2021), 770463.
- [131] B. Krishnamachary, C. Cook, A. Kumar, L. Spikes, P. Chalise, N.K. Dhillon, Extracellular vesicle-mediated endothelial apoptosis and EV-associated proteins correlate with COVID-19 disease severity, *J. Extracell. Vesicles* 10 (2021), e12117.
- [132] Y. Fujita, T. Hoshina, J. Matsuzaki, Y. Yoshioka, T. Kadota, Y. Hosaka, et al., Early prediction of COVID-19 severity using extracellular vesicle COPB2, *J. Extracell. Vesicles* 10 (2021), e12092.
- [133] A.S. Meidert, S. Hermann, F. Brandes, B. Kirchner, D. Buschmann, J.N. Billaud, et al., Extracellular vesicle associated miRNAs regulate signaling pathways involved in COVID-19 pneumonia and the progression to severe acute respiratory corona virus-2 syndrome, *Front. Immunol.* 12 (2021), 784028.
- [134] C. Balbi, J. Burrello, S. Bolis, E. Lazzarini, V. Bielemi, E. Pianezzi, et al., Circulating extracellular vesicles are endowed with enhanced procoagulant activity in SARS-CoV-2 infection, *EBioMedicine* 67 (2021), 103369.
- [135] C. Guervilly, A. Bonifay, S. Burtsey, F. Sabatier, R. Cauchois, E. Abdili, et al., Dissemination of extreme levels of extracellular vesicles: tissue factor activity in patients with severe COVID-19, *Blood Adv.* 5 (2021) 628–634.
- [136] A. Rosell, S. Havervall, F. von Meijenfheldt, Y. Hisada, K. Aguilera, S.P. Grover, et al., Patients with COVID-19 have elevated levels of circulating extracellular vesicle tissue factor activity that is associated with severity and mortality-brief report, *Arterioscler. Thromb. Vasc. Biol.* 41 (2021) 878–882.
- [137] M. Furlan, Von Willebrand factor: molecular size and functional activity, *Ann. Hematol.* 72 (1996) 341–348.
- [138] J.T. Crawley, R. de Groot, Y. Xiang, B.M. Luken, D.A. Lane, Unraveling the scissile bond: how ADAMTS13 recognizes and cleaves von Willebrand factor, *Blood* 118 (2011) 3212–3221.
- [139] K. Fujikawa, H. Suzuki, B. McMullen, D. Chung, Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family, *Blood* 98 (2001) 1662–1666.
- [140] J.D. Roh, R.R. Kitchen, J.S. Guseh, J.N. McNeill, M. Aid, A.J. Martinot, et al., Plasma proteomics of COVID-19-associated cardiovascular complications: implications for pathophysiology and therapeutics, *JACC BasicTransl.Sci.* 7 (2022) 425–441.
- [141] S.E. Ward, H. Fogarty, E. Karampini, M. Lavin, S. Schneppenheim, R. Dittmer, et al., ADAMTS13 regulation of VWF multimer distribution in severe COVID-19, *J. Thromb. Haemost.* 19 (2021) 1914–1921.
- [142] A. Mojiri, P. Alavi, M.A. Lorenzana Carrillo, M. Nakhaei-Nejad, C.M. Sergi, B. Thebaud, et al., Endothelial cells of different organs exhibit heterogeneity in von Willebrand factor expression in response to hypoxia, *Atherosclerosis* 282 (2019) 1–10.
- [143] A. Mojiri, M. Nakhaei-Nejad, W.L. Phan, S. Kulak, A. Radziwon-Balicka, P. Jurasz, et al., Hypoxia results in upregulation and de novo activation of von Willebrand factor expression in lung endothelial cells, *Arterioscler. Thromb. Vasc. Biol.* 33 (2013) 1329–1338.
- [144] A. Bernardo, C. Ball, L. Nolasco, J.F. Moake, J.F. Dong, Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand factor multimers under flow, *Blood* 104 (2004) 100–106.
- [145] R.A. Claus, C.L. Bockmeyer, K. Kentouche, M.W. Sieber, V. Oberle, R. Kaufmann, et al., Transcriptional regulation of ADAMTS13, *Thromb. Haemost.* 94 (2005) 41–45.
- [146] M. Uemura, K. Tatsumi, M. Matsumoto, M. Fujimoto, T. Matsuyama, M. Ishikawa, et al., Localization of ADAMTS13 to the stellate cells of human liver, *Blood* 106 (2005) 922–924.
- [147] Y. Fujimura, L.Z. Holland, COVID-19 microthrombosis: unusually large VWF multimers are a platform for activation of the alternative complement pathway under cytokine storm, *Int. J. Hematol.* 115 (2022) 457–469.
- [148] X. Fu, J. Chen, R. Gallagher, Y. Zheng, D.W. Chung, J.A. Lopez, Shear stress-induced unfolding of VWF accelerates oxidation of key methionine residues in the A1A2A3 region, *Blood* 118 (2011) 5283–5291.
- [149] J. Chen, X. Fu, Y. Wang, M. Ling, B. McMullen, J. Kulman, et al., Oxidative modification of von Willebrand factor by neutrophil oxidants inhibits its cleavage by ADAMTS13, *Blood* 115 (2010) 706–712.
- [150] A. Baiges, E. Cerda, C. Amicone, L. Tellez, E. Alvarado-Tapias, A. Puente, et al., Impact of SARS-CoV-2 pandemic on vascular liver diseases, in: *Clin. Gastroenterol. Hepatol.*, 2021.
- [151] K. Luo, Y. Chen, J. Yang, Q. Tao, M. Luo, Liver injury and elevated levels of interleukins, Interleukin-2 receptor, and Interleukin-6 predict the severity in patients with COVID-19, *Front. Public Health* 9 (2021), 778340.
- [152] G. Wang, Q. Zhang, X. Zhao, H. Dong, C. Wu, F. Wu, et al., Low high-density lipoprotein level is correlated with the severity of COVID-19 patients: an observational study, *Lipids Health Dis.* 19 (2020) 204.
- [153] M.C. Beaulieu, D.S. Mettelus, B. Rioux-Masse, M. Mahone, Thrombotic thrombocytopenic purpura as the initial presentation of COVID-19, *J. Thromb. Haemost.* 19 (2021) 1132–1134.
- [154] M. Capecci, C. Mocellin, C. Abbruzzese, I. Mancini, D. Prati, F. Peyvandi, Dramatic presentation of acquired thrombotic thrombocytopenic purpura associated with COVID-19, *Haematologica* 105 (2020), e540.
- [155] K. Shankar, D.L. Huffman, C. Peterson, M. Yasir, R. Kaplan, A case of COVID-19 induced thrombotic thrombocytopenic purpura, *Cureus* 13 (2021), e16311.
- [156] N. Arulkumaran, M. Thomas, D. Brealey, F. Alwan, D. Singh, M. Lunn, et al., Plasma exchange for COVID-19 thrombo-inflammatory disease, *EJHaem* 2 (2020) 26–32.
- [157] G. Dhingra, M. Maji, S. Mandal, S. Vaniyath, G. Negi, U.K. Nath, COVID 19 infection associated with thrombotic thrombocytopenic purpura, *J. Thromb. Thrombolysis* 52 (2021) 504–507.
- [158] F.S. Seibert, A. Blazquez-Navarro, B. Holzer, A.A.N. Doevelaar, C. Nussbag, U. Merle, et al., Effect of plasma exchange on COVID-19 associated excess of von Willebrand factor and inflammation in critically ill patients, *Sci. Rep.* 12 (2022) 4801.
- [159] C. Masias, S. Vasu, S.R. Cataland, None of the above: thrombotic microangiopathy beyond TTP and HUS, *Blood* 129 (2017) 2857–2863.
- [160] P.L. Turecek, R.C. Peck, S. Rangarajan, C. Reilly-Stitt, M.A. Laffan, R. Kazmi, et al., Recombinant ADAMTS13 reduces abnormally up-regulated von Willebrand factor in plasma from patients with severe COVID-19, *Thromb. Res.* 201 (2021) 100–112.
- [161] M. Scully, S.R. Cataland, F. Peyvandi, P. Coppo, P. Knobl, J.A. Kremer Hovinga, et al., Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura, *N. Engl. J. Med.* 380 (2019) 335–346.
- [162] F. Peyvandi, S. Cataland, M. Scully, P. Coppo, P. Knoebel, J.A. Kremer Hovinga, et al., Caplacizumab prevents refractoriness and mortality in acquired thrombotic thrombocytopenic purpura: integrated analysis, *Blood Adv.* 5 (2021) 2137–2141.
- [163] S.R. Cataland, F. Peyvandi, P.M. Mannucci, B. Lammle, J.A. Kremer Hovinga, S. J. Machin, et al., Initial experience from a double-blind, placebo-controlled, clinical outcome study of ARC1779 in patients with thrombotic thrombocytopenic purpura, *Am. J. Hematol.* 87 (2012) 430–432.
- [164] K. Sakai, T. Someya, K. Harada, H. Yagi, T. Matsui, M. Matsumoto, Novel aptamer to von Willebrand factor A1 domain (TAGX-0004) shows total inhibition of thrombus formation superior to ARC1779 and comparable to caplacizumab, *Haematologica* 105 (2020) 2631–2638.
- [165] S. Zhu, J.C. Gilbert, P. Hatala, W. Harvey, Z. Liang, S. Gao, et al., The development and characterization of a long acting anti-thrombotic von Willebrand factor (VWF) aptamer, *J. Thromb. Haemost.* 18 (2020) 1113–1123.

- [166] J. Chen, A. Rehemian, F.C. Gushiken, L. Nolasco, X. Fu, J.L. Moake, et al., N-acetylcysteine reduces the size and activity of von Willebrand factor in human plasma and mice, *J. Clin. Invest.* 121 (2011) 593–603.
- [167] J.L. Izquierdo, J.B. Soriano, Y. Gonzalez, S. Lumbreras, J. Ancochea, C. Echeverry, et al., Use of N-acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19, *Sci. Prog.* 105 (2022), 368504221074574.
- [168] S. De Flora, R. Balansky, S. La Maestra, Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19, *FASEB J.* 34 (2020) 13185–13193.
- [169] F. Di Marco, G. Foti, A.G. Corsico, Where are we with the use of N-acetylcysteine as a preventive and adjuvant treatment for COVID-19? *Eur. Rev. Med. Pharmacol. Sci.* 26 (2022) 715–721.
- [170] S.E. Ward, J.M. O'Sullivan, J.S. O'Donnell, The relationship between ABO blood group, von Willebrand factor, and primary hemostasis, *Blood* 136 (2020) 2864–2874.