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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...
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 endotheiiitis) 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, multiorgan 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 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 protease”)) 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 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). I² statistics was used to evaluate the data heterogeneity. Outcomes with I² > 50 % were regarded as having a high heterogeneity. The random-effects model was used to analyze outcomes for included studies when I² > 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
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; I² = 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; I² = 77%), ICU need (SMD = 0.96 95%CI [1.30, 0.62], p < 0.00001; I² = 61%) or high severity (SMD = 1.18 95%CI [1.59, 0.77], p < 0.00001; I² = 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; I² = 87%; Fig. 3). They were also significantly higher in ICU-patients (SMD = −0.85 95%CI [−1.20, −0.50], p < 0.00001; I² = 21%) and severe patients (SMD = −1.29 95%CI [−2.30, −0.29], p = 0.001; I² = 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 [0.80, 0.75], p < 0.00001; I² = 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; I² = 55%), ICU admission and non-ICU admission (SMD = 0.72 95%CI [0.31, 1.13], p = 0.0006; I² = 60%), and severe status and non-severe status (SMD = 0.76 95%CI [0.34, 1.19], p = 0.0004; I² = 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; I² = 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; I² = 82%), ICU admission (SMD = −0.96 95%CI [−1.27, −0.64], p < 0.00001; I² =
| Study           | Country          | Design                        | Period                                      | Total | Gender, n (Female/Male) | Favorable clinical outcomes | Unfavorable clinical outcomes | VWF-related variables | Quality (NOS) |
|-----------------|------------------|-------------------------------|---------------------------------------------|-------|-------------------------|-----------------------------|-------------------------------|------------------------|---------------|
| Bauer et al.    | Germany          | Prospective; Single center    | March 2020–June 2020                        | 17    | 11/6                    | ICU admission              | 71.9 (IQR, 57.5–76.8)       | 5/2                    | 8             |
| Bazzan et al.   | Italy            | Retrospective; Single center  | N/A                                         | 88    | N/A                     | ICU admission              | 10 (IQR, 63.7–71.0)         | 9                      | 7             |
| Blasi et al.    | Spain            | Prospective; Single center    | April 2020                                  | 23    | 9/14                    | ICU admission              | 11 (IQR, 58–62)             | 25/54                   | 3/6           |
| Cugno et al.    | Italy            | Prospective; Single center    | March 1, 2020–April 15, 2020                | 104   | N/A                     | Severity                   | 58 (IQR, 42–76)             | 46/6                    | 7             |
| De Jongh et al. | Netherlands      | Cross-sectional; Single center| N/A                                         | 16    | N/A                     | Mortality                  | 11 (IQR, 62.5–13.7)         | 7                      | 7             |
| Delrue et al.   | France           | Prospective; Single center    | March 17, 2020–April 11, 2020               | 133   | 97/26                   | Mortality                  | 110 (IQR, 58–60)            | 23                     | 5             |
| Doevelaar et al.| Germany          | Prospective; Single center    | N/A                                         | 75    | 38/37                   | Mortality                  | 62 (IQR, 15–61)             | 13                     | 6             |
| Dupont et al.   | France           | Prospective; Single center    | March 21, 2020–April 16, 2020               | 82    | 18/64                   | Mortality                  | 60 (IQR, 71–86)             | 22                     | 9             |
| Dushianthan et al. | GBR             | Retrospective; Single center  | March 2020–March 2021                       | 65    | N/A                     | Mortality                  | 54 (IQR, 71–86)             | N/A                    | 7             |
| Fan et al.      | Singapore        | Prospective; Multi-center     | June 2020–January 2021                      | 20    | 4/16                    | Severity                   | 10 (IQR, 60–65)             | 10                     | 8             |
| Fernández et al.| Spain            | Prospective; Single center    | May 1, 2020–May 31, 2020                    | 34    | N/A                     | Severity                   | 24 (IQR, 31–71)             | 10                     | 7             |
| Francischetti et al. | United States | Cross-sectional; Single center | April 2020–October 2020                    | 66    | 33/33                   | Severity                   | 40 (IQR, 17–65)             | 21                     | 7             |
| Godhwa et al.   | United States    | Cross-sectional; Single center| April 13, 2020–April 24, 2020              | 68    | 27/41                   | ICU admission              | 20 (IQR, 58–65)             | 48                     | 12/8          |
| Helin et al.    | Finland          | Retrospective; Single center  | April 2020–May 2020                         | 78    | 34/44                   | ICU admission              | 44 (IQR, 58–65)             | 34                     | 5             |
| Henry et al.    | United States    | Prospective; Single center    | April 2020–May 2020                         | 52    | 22/30                   | Severity                   | 36 (IQR, 60–64)             | 16                     | 6             |
| Herr et al.     | Germany          | Prospective; Multi-center     | March 2020–July 2020                        | 35    | 24/26                   | Mortality                  | 61.96 ± 3.18 (IQR, 39–66)   | N/A                    | 7             |
| Joly et al.     | France           | Prospective; Single center    | March 18, 2020–May 9, 2020                 | 53    | 14/39                   | Mortality                  | 38 (IQR, 59–66)             | 15                     | 7             |
| Study                        | Country    | Design               | Period                                      | Total Size | Age (year) | Gender, n (Female/Male) | Favorable clinical outcomes | Unfavorable clinical outcomes |
|------------------------------|------------|----------------------|---------------------------------------------|------------|------------|------------------------|-----------------------------|-------------------------------|
| 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                         |
| Lichter et al               | Israel     | Retrospective; Single center | April 26, 2020-July 4, 2021                 | 39         | N/A        | ICU admission           | 5 N/A                       | N/A 34 (Range, 22–76)         |
| Lopez-Castaneda et al       | Mexico     | Prospective; Single center | July 2020-September 2020                    | 55         | N/A        | Severity               | 37 44.52 ± 12.7             | 11/26 63.77 ± 13.8 9/9 VWF: Ag |
| Mancini et al               | Italy      | Retrospective; Single center | March 2020-mid-April 2020                  | 33         | N/A        | Severity               | 14 58 (Range, 27–85)        | 7/7 59 (Range, 40–71) 6/13    |
| 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                        |
| Marco et al                 | Spain      | Prospective; Single center | April 2020- May 2020                       | 152        | N/A        | Mortality              | 143 N/A                     | N/A 9                         |
| Martín-Rojas et al          | Spain      | Retrospective; Single center | April 2020                                    | 62         | 61.8 ± 15.2 | 10/43             | 51 61.2 ± 15.4             | 16/35 64.7 ± 14.9 3/8 VWF: Ag |
| Martín-Rojas et al          | Spain      | Retrospective; Single center | April 3, 2020-May 3, 2020                   | 206        | 63.6 ± 13.4 | 75/13             | 188 62.4 ± 12.9            | 64/120 76.0 ± 12.3 7/11 VWF: Ag |
| Montiel et al               | Belgium    | Prospective; Single center | April 27, 2020-November 3, 2020            | 60         | N/A        | Mortality              | 30 52.1 ± 13.5             | 8/22 61.3 ± 8.7 5/25 VWF: Ag |
| Nougier et al               | France     | Prospective; Single center | N/A                                          | 78         | 60.2 ± 14.4 | 27/51             | 30 60.2 ± 14.6             | N/A 48                         |
| Pascreau et al              | France     | Prospective; Single center | N/A                                          | 70         | 66         | N/A                   | 55 N/A                      | N/A 15                         |
| Philippe et al              | France     | Prospective; Multi-center Cross-sectional; Single center | March 13, 2020-June 26, 2020                | 185        | N/A        | Severity               | 96 65.5 (IQR, 55.0–76.0)   | 41/55 62.0 (IQR, 51.0–71.0) 24/65 |
| Philippe et al              | France     | Prospective; Single center | N/A                                          | 77         | N/A        | Severity               | 37 63 (IQR, 52–72)          | 12/25 62 (IQR, 53–72) 7/33    |
| Rauch et al                 | France     | Prospective; Single center | March 20, 2020-April 17, 2020               | 243        | 63.9 ± 16.2 | 88/155             | 211 N/A                     | N/A 32                         |
| Rodríguez et al             | France     | Retrospective; Single center | March 15, 2020-April 1, 2020                | 100        | 60.5       | Mortality              | 81 N/A                      | N/A 19                         |
| Sinkovits et al             | Hungary    | Prospective; Single center | April 20, 2020-July 2, 2020                | 102        | 67 (IQR, 56–76) | 46/56             | 77 N/A                      | N/A 25                         |

(continued on next page)
| Study               | Country     | Design                  | Period                                    | Total                          | Favorable clinical outcomes | Unfavorable clinical outcomes |
|---------------------|-------------|-------------------------|-------------------------------------------|-------------------------------|-----------------------------|-----------------------------|
|                     |             |                         |                                           | Size  | Age (year) | Gender, n (Female/Male) | Size  | Age (year) | Gender, n (Female/Male) | Size  | Age (year) | Gender, n (Female/Male) | VWF-related variables | Quality |
| Sweeney et al.      | United States | Retrospective; Single center | March 26, 2020-March 5, 2020 | 181   | N/A        | N/A   | Mortality 91          | 62.0 (IQR, 50.5-70.0) | 45/46 | 72.5 (IQR, 63.3-79.8) | 30/60 |
|                     | United States | Retrospective; Single center | April 14, 2020-May 12, 2020 | 543   | 63 (Range, 3.0-99) | N/A   | Mortality 433         | N/A     | N/A   | N/A     | N/A  |
|                     | India       | Prospective; Single center | July 22, 2020-August 3, 2020 | 71    | N/A        | N/A   | Severity 34           | 35.5 (IQR, 29-49)     | 12/22 | 57 (IQR, 49-62)     | 3/34  |
|                     | 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 | 63.0 (IQR,15.2)     | 5/17  |
| 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 | 54.50 (IQR, 46.75-60.75) | 6/30 |
| Vassiliou et al.    | Greece      | Prospective; Single center | March 2020-October 25, 2020 | 38    | 63 ±11     | 7/31  | Mortality 28          | 62 ±11  | 5/23 | 68 ±10  | 2/8  |
| von Meijenfeldt et al. | Sweden       | Prospective; Single center | April 9, 2020-June 8, 2020 | 102   | N/A        | N/A   | Mortality 92          | N/A     | N/A   | N/A     | N/A  |

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.
0 %), and severe disease (SMD = −0.96 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 [0.105, 0.23], 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 [0.127, 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...
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

**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 | I² |
|---------|-----------|---------------------------|-----------------------------------------------|-----------------------------------------------|-----------------|-----------------------------------|---------|-----|
|         | Mortality | 17                        | 1538                                          | 457                                           | 1995            | -0.79 [-1.05, -0.52]              | p < 0.00001% | 77% |
|         | ICU       | 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       | 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       | 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       | 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       | 8                         | 373                                           | 255                                           | 628             | -0.81 [-1.15, -0.47]              | p < 0.00001% | 67% |

Abbreviations: ADAMTS13: Ac, a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13; Activity; CI, confidence interval; FVIII, factor VIII; ICU, Intensive 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.
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. 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.
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 [42,106,107]. However, whether these variables can be used for prospective clinical assessments may require further studies.

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-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 stored in Weibel-Palade bodies (WPBs) of ECs and α-granules of platelets (via A1 domain) - 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 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 associated 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 VWF, whereas ECs of 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 contribute to the marked increase in 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 persistent 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 VWF:Ag (mainly synthesized in hepatocytes [119]) in COVID-19 patients [78,114] may be 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 VWF:Ag (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) platelet-platelet interactions with platelet receptor glycoprotein (GP) Ibα via A1 domain) and subendothelial collagen (via A3 domain); 2) platelet-platelet

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**Fig. 6.** Forest plot of the association between FVIII and composite clinical outcomes.
interaction (platelet aggregation) by binding to platelet receptor GPIb/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) supporting 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 is 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, Ackerman 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]. Increasing 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 monomer 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; Try1605-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 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 patients have observed evidence of increased ULVWF [76,81]. The differences likely due to the study cohort recruitment, time of sample collection, and the methodologies of VWF multimer determination [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 EGs [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 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 thrombosis 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 pathophysiologic 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 GPIbα 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], TARGX-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 N-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

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

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