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Biomarkers of endothelial dysfunction and outcomes in coronavirus disease 2019 (COVID-19) patients: A systematic review and meta-analysis

Andrianto [a,*], Makhyan Jibril Al-Farabi [a], Ricardo Adrian Nugraha [a], Bagas Adhimurda Marsudi [b], Yusuf Azmi [c]

[a] Department of Cardiology and Vascular Medicine, Soetomo General Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya 60286, Indonesia
[b] Department of Cardiology and Vascular Medicine, National Cardiovascular Center Harapan Kita, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[c] Faculty of Medicine, Universitas Airlangga, Surabaya 60286, Indonesia

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ABSTRACT

Background: Several studies have reported that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can directly infect endothelial cells, and endothelial dysfunction is often found in severe cases of coronavirus disease 2019 (COVID-19). To better understand the prognostic values of endothelial dysfunction in COVID-19-associated coagulopathy, we conducted a systematic review and meta-analysis to assess biomarkers of endothelial cells in patients with COVID-19.

Methods: A literature search was conducted on online databases for observational studies evaluating biomarkers of endothelial dysfunction and composite poor outcomes in COVID-19 patients.

Results: A total of 1187 patients from 17 studies were included in this analysis. The estimated pooled means for von Willebrand Factor (VWF) antigen levels in COVID-19 patients was higher compared to healthy control (306.42 [95% confidence interval (CI) 291.37–321.48], $p < 0.001$; I^2:86%), with the highest VWF antigen levels was found in deceased COVID-19 patients (448.57 [95% CI 407.20–489.93], $p < 0.001$; I^2:0%). Meta-analysis showed that higher plasma levels of VWF antigen, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 antigen (PAI-1) antigen, and soluble thrombomodulin (sTM) were associated with composite poor outcome in COVID-19 patients ([standardized mean difference (SMD) 0.74 [0.33–1.16], $p < 0.001$; I^2:80.4%], [SMD 0.55 [0.19–0.92], $p = 0.003$; I^2:6.4%], [SMD 0.33 [0.04–0.62], $p = 0.025$; I^2:7.9%], and [SMD 0.55 [0.10–0.99], $p = 0.015$; I^2:23.6%], respectively).

Conclusion: The estimated pooled means show increased levels of VWF antigen in COVID-19 patients. Several biomarkers of endothelial dysfunction, including VFW antigen, t-PA, PAI-1, and sTM, are significantly associated with increased composite poor outcomes in patients with COVID-19.

PROSPERO registration number: CRD42021228821

1. Introduction

Although initially recognized as a disease affecting the respiratory system, coronavirus disease 2019 (COVID-19) often manifests as cardiovascular complications such as myocarditis, myocardial injuries, arrhythmias, and venous thromboembolism events (VTE) (Evans et al., 2020). There are several possible mechanisms for these phenomena, one of which may be an unrestrained and unbalanced innate immune response, which in turn negates effective adaptive immunity, supporting the progression of COVID-19. Frequent laboratory abnormalities in patients with unfavorable progression of COVID-19, including abnormal cytokine profiles, led to the initial presumption that the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection involved a cytokine storm (Perico et al., 2020). However, recent evidence suggests that increased inflammatory cytokines including interleukin-6 (IL-6) in patients with severe and critical COVID-19 are significantly lower compared to patients with sepsis and acute respiratory distress syndrome (ARDS) not associated with COVID-19,

* Corresponding author at: Department of Cardiology and Vascular Medicine, Soetomo General Hospital, Faculty of Medicine, Universitas Airlangga, Mayjen Prof. Dr. Moestopo Street No.47, Surabaya 60132, Indonesia.
E-mail addresses: andrianto@fk.unair.ac.id (Andrianto), m.farabi.17@ucl.ac.uk (M.J. Al-Farabi), ricardo.adrian.nugraha-2019@fk.unair.ac.id (R.A. Nugraha), yusuf.azmi-13@fk.unair.ac.id (Y. Azmi).

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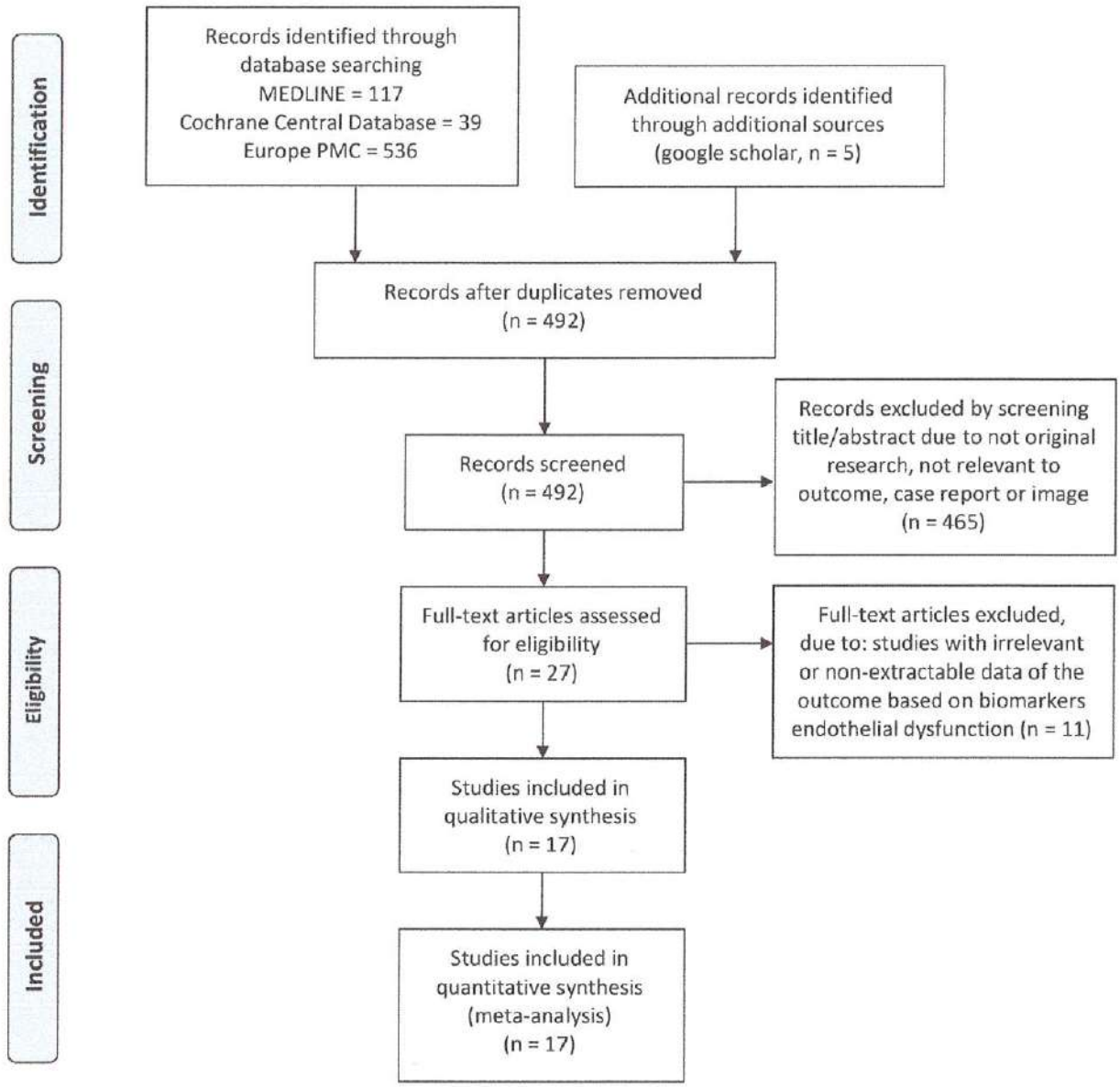

Fig. 1. PRISMA flowchart.

thus doubting the role of a cytokine storm in COVID-19-related multiple organ damage (Leisman et al., 2020).

Several studies have reported that the SARS-CoV-2 can directly infect endothelial cells, and endothelial dysfunction is often found in severe cases of COVID-19 (Nägele et al., 2020). Autopsy findings have also demonstrated endothelial dysfunction and microvascular thrombosis together with pulmonary embolism (PE) and deep-vein thrombosis in COVID-19 patients (Gavriilaki et al., 2020). These findings suggest that endothelial injury, endotheliitis, and microcirculatory dysfunction in different vascular beds contribute significantly to life-threatening complications of COVID-19, such as VTE and multiple organ involvement (Huertas et al., 2020). To better understand the prognostic values of endothelial dysfunction in COVID-19-associated coagulopathy, we conducted a systematic review and meta-analysis to assess biomarkers of endothelial cells in patients with COVID-19.

2. Methods

2.1. Search strategy and study selection

A systematic literature search of PubMed, PMC Europe, and the Cochrane Library Database from 1 January 2020 to 20 December 2020 was performed using the search strategy outlined in Supplementary Table S1. Additional records were retrieved from Google Scholar. Duplicate articles were removed after the initial search. Two authors (MJA and YA) independently screened the title and abstract of the articles. Articles that passed the screening were assessed in full text based on the eligibility criteria. Disagreements were resolved by discussion with the senior author (A). This study was conducted following the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) statement and registered with the International Prospective

Table 1
Characteristics of the included studies.

No	Study	Population	Study location	No. of samples	Age mean (SD)	Male n (%)	DM n (%)	HT n (%)	Hyper-lipidemia n (%)	Comparison/end point measure	Marker examined	NOS
1	Cugno et al. (2020)	All hospitalized patients	Italy	148	61 (13)	87 (59)	NA	NA	NA	ICU admission	VWF antigen, sTM, PAI-1 antigen, t-PA	8
2	Fan et al. (2020)	ICU patients	Singapore	12	51 (17)	11 (92)	5 (42)	6 (50)	4 (33)	NA	VWF antigen	6
3	Goshua et al. (2020)	All hospitalized patients	United States	68	62 (16)	41 (60)	20 (29)	38 (56)	18 (26)	ICU admission	VWF antigen, sTM, PAI-1 antigen	9
4	Helms et al. (2020)	ICU patients	France	150	62 (14)	122 (81)	30 (20)	NA	NA	NA	VWF antigen	6
5	Henry et al. (2020)	All hospitalized patients	United States	52	52 (21)	30 (58)	21 (40)	26 (50)	15 (29)	Severe COVID-19	VWF antigen	9
6	Hoechter et al. (2020)	ICU patients	Germany	22	62 (14)	19 (86)	NA	NA	NA	NA	VWF antigen	7
7	Ladikou et al. (2020)	ICU patients	United Kingdom	24	64 (13)	18 (75)	NA	NA	NA	ICU admission	VWF antigen	7
8	Mancini et al. (2020)	All hospitalized patients	Italy	50	58 (13)	32 (64)	4 (8)	14 (28)	NA	ICU admission	VWF antigen	7
9	Morici et al. (2020)	ICU patients	Italy	6	62 (5)	4 (67)	1 (17)	2 (33)	NA	NA	VWF antigen	6
10	Nougier et al. (2020)	All hospitalized patients	France	78	60 (14)	51 (65)	NA	NA	NA	ICU admission	PAI-1 antigen, t-PA	9
11	Panigada et al. (2020)	ICU patients	Italy	24	56 (15)	NA	NA	NA	NA	NA	VWF antigen	6
12	Pine et al. (2020)	All hospitalized patients	United States	49	63 (17)	33 (67)	13 (27)	30 (61)	12 (25)	ICU admission	PAI-1 antigen	8
13	Ranucci et al. (2020)	ICU patients	Italy	20	64 (12)	16 (80)	5 (25)	6 (30)	NA	Mortality	t-PA	8
14	Rauch et al. (2020)	All hospitalized patients	France	243	64 (16)	155 (64)	56 (23)	118 (49)	NA	Worsening of the respiratory status	VWF antigen	7
15	Rovas et al. (2020)	All hospitalized patients	Germany	23	64 (17)	20 (87)	0	15 (65)	NA	Mechanical ventilator	sTM	9
16	Sweeney et al. (2020)	All hospitalized patients	United States	181	66 (15)	106 (59)	NA	NA	NA	Mortality	VWF antigen	7
17	Taus et al. (2020)	All hospitalized patients	Italy	37	62 (13)	18 (49)	0	21 (57)	NA	NA	VWF antigen, VWF activity	8

DM, diabetes mellitus; HT, hypertension; ICU, intensive care unit; NA, not available; VWF, von Willebrand Factor; PAI-1, plasminogen activator inhibitor-1 antigen; sTM, soluble thrombomodulin; t-PA, tissue-type plasminogen activator; NOS, Newcastle-Ottawa Scale; SD, standard deviation; n, number; %, percentage.

Register of Systematic Reviews (PROSPERO) database (registration number CRD42021228821).

2.2. Eligibility criteria

We included all observational studies examining biomarkers of endothelial dysfunction and outcomes from patients who tested positive for SARS-CoV-2 using the reverse transcription-polymerase chain reaction (RT-PCR) test. The following types of articles were excluded from the analysis: case reports, review articles, 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 collection process

Data extraction was carried out by two authors (MJA and YA) independently using piloted data extraction forms consisting of the author, year of publication, study design, number and characteristics of samples, levels of several biomarkers of endothelial dysfunction, and patient outcomes. The biomarkers of endothelial dysfunction analyzed in this study were von Willebrand Factor (VWF) antigen, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 antigen (PAI-1), and soluble thrombomodulin (sTM). The primary endpoint was composite poor outcomes consisting of ICU admission, severe illness, worsening of the respiratory status, the need for mechanical ventilation, and mortality. Moreover, if the included studies reported the data using median and quartile values, we used the formula developed by Wan et al. to estimate mean and standard deviation (Wan et al., 2014). Disease severity was defined based on the WHO R&D Blueprint on COVID-19 (World Health Organization, 2020).

2.4. Quality assessment

The quality and risk of bias assessment of included studies were conducted using the Newcastle-Ottawa score (NOS) (Wells et al., 2015) by all authors independently, and discrepancies were resolved through discussion. This scoring system consists of three domains: the selection of sample cohorts, comparability of cohorts, and assessment of outcomes (Supplementary Table S2).

2.5. Data analysis

Stata software V.14.0 (College Station) was used for meta-analysis, and figure of estimated pooled means were produced using GraphPad Prism 9. We pooled multiple means and standard errors of the same population characteristic from different studies into a single group using the fixed-effect model of the meta-analysis algorithm. Pooled effect estimates of the outcomes were reported as standardized means differences (SMD). Fixed-effects and random-effects models were used for pooled analysis with low heterogeneity (I^2 statistic <50% or p-value <0.1) and high heterogeneity (I^2 statistic>50% or p-value ≤0.1), respectively. Statistical significance was determined with p-value <0.05. We performed a sensitivity analysis to test the robustness of the

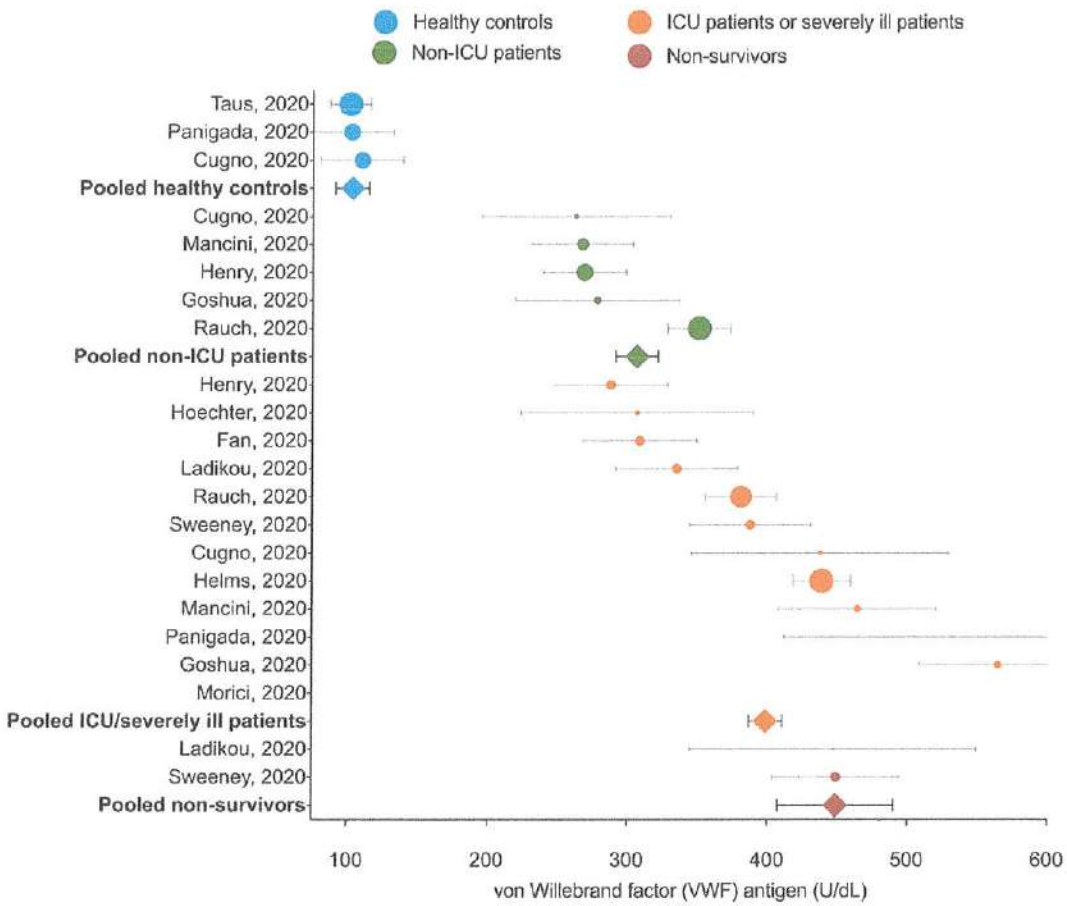

Fig. 2. The estimated pooled mean for plasma levels of von Willebrand Factor antigen in patients with COVID-19. For individual studies, circle markers indicate study means and error bars indicate 95% confidence intervals. Markers are sized proportionately to the weight of the study in the analysis. Estimated pooled means for grouped studies are represented by the square markers.

pooled effect estimates for VWF antigen levels by excluding each study sequentially and rerunning the meta-analysis. The funnel-plot analysis was used to assess the symmetrical distribution of effect sizes, and the regression-based Egger test was performed to assess publication bias on continuous endpoints.

3. Results

3.1. Study characteristics

We identified 697 articles from the database search, and 492 articles remained after the duplication was removed. Screening on titles and abstracts excluded 465 articles, and the remaining 27 full-text articles were assessed according to eligibility criteria. As a result, 17 studies (Cugno et al., 2020; Fan et al., 2020; Goshua et al., 2020; Helms et al., 2020; Henry et al., 2020; Hoechter et al., 2020; Ladikou et al., 2020; Mancini et al., 2020; Morici et al., 2020; Nougier et al., 2020; Panigada et al., 2020; Pine et al., 2020; Ranucci et al., 2020; Rauch et al., 2020; Rovas et al., 2020; Sweeney et al., 2020; Taus et al., 2020) with a total of 1187 patients were subjected to qualitative analysis and meta-analysis (Fig. 1 and Table 1). Quality assessment with NOS showed that 13 studies (Cugno et al., 2020; Goshua et al., 2020; Henry et al., 2020; Hoechter et al., 2020; Ladikou et al., 2020; Mancini et al., 2020; Nougier et al., 2020; Pine et al., 2020; Ranucci et al., 2020; Rauch et al., 2020; Rovas et al., 2020; Sweeney et al., 2020; Taus et al., 2020) were of good quality with ≥7 NOS score and four studies (Fan et al., 2020; Helms et al., 2020; Morici et al., 2020; Panigada et al., 2020) were considered as moderate quality with six NOS score (Supplementary Table S2).

3.2. Biomarkers of endothelial dysfunction and outcome

There was an increase in the VWF antigen levels in COVID-19 patients with different levels for each outcome group of COVID-19 patients. The pooled means plasma levels of VWF antigen in COVID-19 patients treated at the general wards and ICU patients or severely ill patients ([306.42 [95% confidence interval (CI) 291.37–321.48], $p < 0.001$; I^2:86%] and [398.56 [95% CI 386.84–410.30], $p < 0.001$; I^2:92%], respectively) were higher than healthy controls (103.24 [95% CI 91.31–115.17], $p < 0.001$; I^2:0%). Moreover, deceased COVID-19 patients had the highest pooled means of VWF antigen levels (448.57 [95% CI 407.20–489.93], $p < 0.001$; I^2:0%) (Fig. 2).

Meta-analysis showed that higher plasma levels of VWF antigen were associated with composite poor outcome (SMD 0.74 [0.33–1.16], $p < 0.001$; I^2:80.4%). Patients with poor outcome had significantly a higher level of t-PA and PAI-1 antigen compared to patients with good outcomes ([SMD 0.55 [0.19–0.92], $p = 0.003$; I^2:6.4%] and [SMD 0.33 [0.04–0.62], $p = 0.025$; I^2:7.9%], respectively). The plasma levels of sTM were found to be higher in COVID-19 patients with poor outcome ([SMD 0.55 [0.10–0.99], $p = 0.015$; I^2:23.6%]) (Fig. 3).

We found substantial heterogeneity for VWF antigen analysis (I^2:80.4%) and low heterogeneity for t-PA, PAI-1 antigen, and sTM analysis (I^2:6.4%, I^2:7.9%, and I^2:23.6%, respectively). However, subgroup analyses to evaluate potential sources of heterogeneity of VWF levels were not performed due to the small amount of primary data included in the group analysis. The sensitivity analysis of VWF levels after excluding two studies (Goshua et al., 2020; Mancini et al., 2020) at risk of bias decreased the heterogeneity considerably while maintaining

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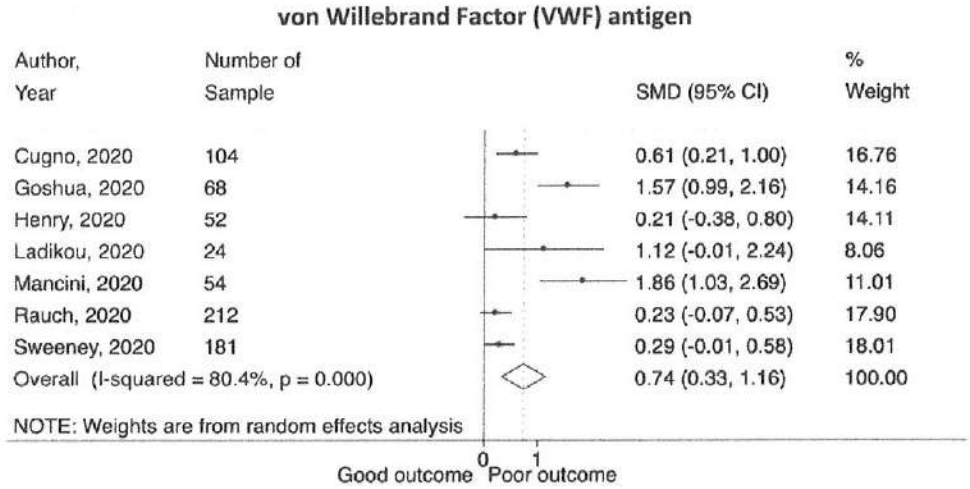

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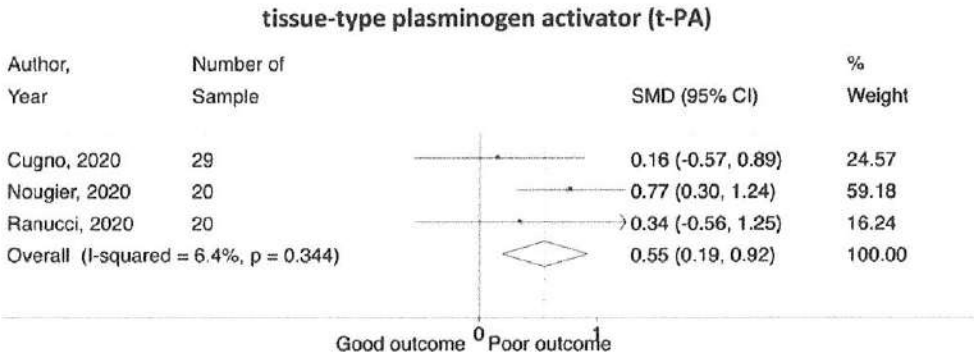

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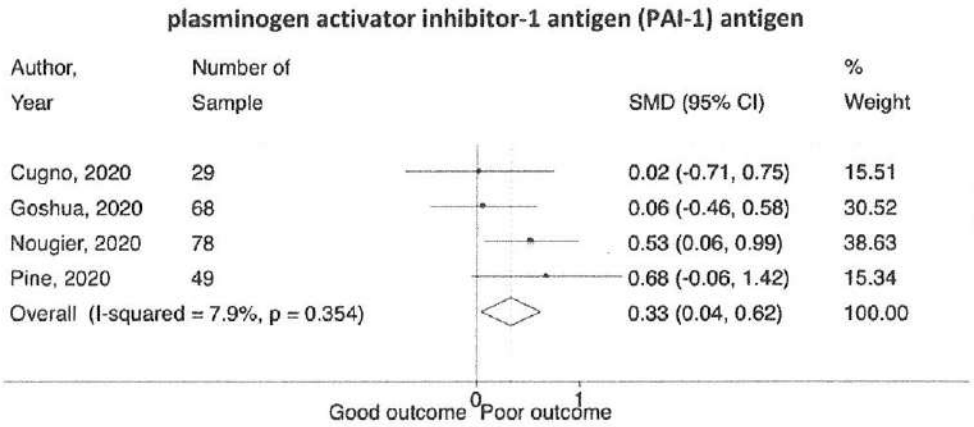

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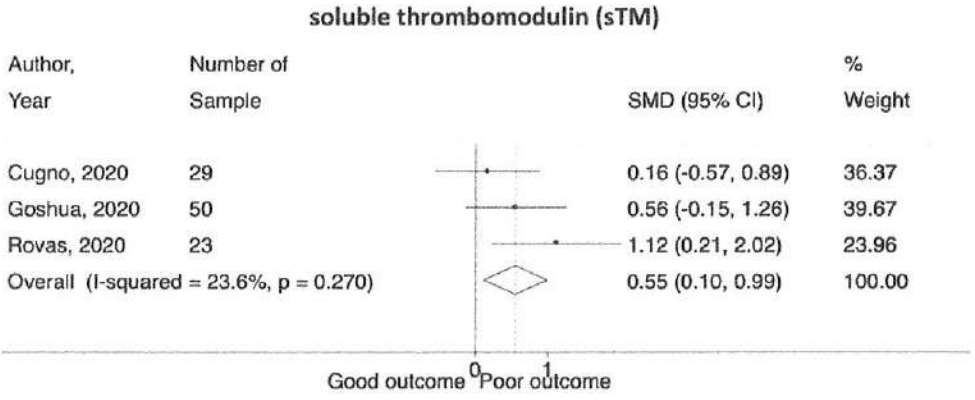

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Fig. 3. Several biomarkers for endothelial dysfunction and the outcome of COVID-19. Patients presenting with a higher plasma levels of (A) von Willebrand Factor (VWF) antigen; (B) tissue-type plasminogen activator (t-PA); (C) plasminogen activator inhibitor-1 antigen (PAI-1) antigen; and (D) soluble thrombomodulin (sTM) have an increased risk of composite poor outcome.

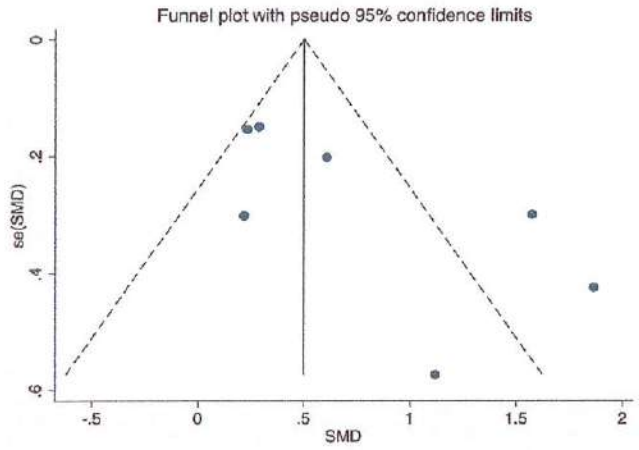

Fig. 4. Funnel-plot analysis for the analysis of the von Willebrand Factor (VWF) antigen. SMD, standardized mean difference.

the significance of pooled effect estimate (SMD 0.34 [0.17–0.62], $p < 0.001$; I2:9.2%).

3.3. Publication bias

The visual assessment of the funnel plot showed an asymmetrical shape for the analysis of the vWF antigen levels, which indicated the possibility of publication bias (Fig. 4). This asymmetrical shape was due to the inclusion of the studies by Goshua et al. (2020) and Mancini et al. (2020). However, quantitative analysis using regression-based Egger's test for the same variable showed no significant result of small-study effects ($p = 0.063$). Regression-based Harbord's test for other biomarkers and composite poor outcome also showed no significant result of small-study effects.

4. Discussion

A single layer of healthy endothelial cells lines the entire vascular system and plays essential roles in maintaining laminar blood flow (Wang et al., 2018). Conditions that cause endothelial activation, such as infection and inflammation, support proatherogenic mechanisms by stimulating thrombin formation, coagulation, and fibrin deposition in blood vessel walls (Lilly, 2012). Activated endothelial cells promote coagulation and induce thrombosis by favoring the expression of antifibrinolytics (e.g., PAI-1) and procoagulants (e.g., tissue factor) over the expression of profibrinolytic mediators (e.g., t-PA) and anticoagulants (e.g., heparin-like molecules and thrombomodulin) (Lilly, 2012; Radermecker et al., 2020; Teuwen et al., 2020). Taken together, these mechanisms contribute to massive platelet binding and formation of fibrin, leading to deposition of blood clots in the microvasculature and systemic thrombosis (Perico et al., 2020). Since viral RNA of SARS-CoV-2 is rarely detected in the blood (Wölfel et al., 2020), it suggests that rather than direct viral infection of endothelial cells, additional host-dependence factors may contribute to systemic endothelial dysfunction and vasculopathy in COVID-19.

von Willebrand Factor (VWF) is a large multidomain adhesive glycoprotein produced by megakaryocytes and endothelial cells (Löf et al., 2018). Endothelial activation in COVID-19 infection and elevated VWF levels as an acute-phase protein released from endothelial cells are recognized as a response to inflammation, but high levels of VWF, in this case, indicate suspicion of endothelial disturbance (Breakey and Escher, 2020). Expression of VWF and its release from the Weibel-Palade body of endothelial cells may also be stimulated by hypoxia. Hypoxia-induced upregulation of VWF is associated with thrombus in cardiac and pulmonary vessels that promote leukocyte recruitment (Mojiri et al., 2019). Several studies have shown that COVID-19 patients have higher plasma levels of VWF antigen than healthy controls (Blasi et al., 2020; Cugno et al., 2020; Panigada et al., 2020; Taus et al., 2020). Elevated levels of the VWF antigen in COVID-19 patients are similar to those reported in studies on patients with disseminated intravascular coagulation (Habe et al., 2012), severe sepsis, and septic shock not associated with COVID-19 (Fukushima et al., 2013; Kremer Hovinga et al., 2007). In addition to the VWF antigen, VWF activity has been shown to increase in COVID-19 patients, thus further explaining the role of endothelial cell injury in COVID-19-associated coagulopathy (Helms et al., 2020; Hoechter et al., 2020; Panigada et al., 2020; Taus et al., 2020).

The procoagulant state resulting from endothelial activation can also be measured from changes in the balance between the levels of t-PA and PAI-1 (Shapiro et al., 2010). Although t-PA is recognized as a profibrinolytic mediator, t-PA is found to be higher in COVID-19 patients with poor outcomes. This paradox may be explained by a study showing that PAI-1, a major inhibitor of t-PA, facilitates the dissociation of t-PA from the surface of vascular endothelial cells (VES), which would therefore decrease cell surface-associated fibrinolytic potential (Suzuki et al., 2009). Decreased amounts of t-PA on the VEC surface and increased concentration of t-PA in the plasma due to increased PAI-1 plasma level may be the possible mechanism of hypofibrinolysis that leads to poor outcomes in COVID-19 patients.

PAI-1 is one of the acute-phase proteins that is increased during inflammatory disorders where the concentrations are affected by the changes in its production by hepatocytes (Gabay and Kushner, 1999). In patients with ARDS, increased levels of PAI-1 produced by endothelial cells and lung epithelium are associated with severe hypofibrinolytic state (Whyte et al., 2020). In addition to endothelial activation due to proinflammatory cytokines, binding of SARS-CoV-2 to the ACE2 receptor induces enhanced shredding of ACE2, thereby increasing Ang II levels which further stimulates PAI-1 expression in various cells including, endothelial cells, adipocytes, and smooth muscle cells (Gue and Gorog, 2020). In COVID-19 patients, plasma levels of PAI-1 were found to be 3.7 times higher than in healthy controls (Blasi et al., 2020). Furthermore, COVID-19 patients with severe respiratory dysfunction show significantly higher levels of PAI-1 compared to patients with burns, ARDS, and sepsis (Kang et al., 2020).

Soluble thrombomodulin (sTM) is a product of proteolytic cleavage of the intact thrombomodulin protein from the surface of endothelial cells after endothelial injury and dysfunction (Martin et al., 2013). In the hyperinflammatory state, increased sTM levels could be due to direct damage to the endothelial cells (Nawroth and Häring, 1999). Elevated plasma levels of sTM have also been reported in patients with the severe acute respiratory syndrome (SARS), indicating endothelial injury (Liu et al., 2005). The plasma levels of sTM might be too low to impact the coagulation process, but the consistent increase in sTM levels during pathologies has been widely considered a biomarker for endothelial dysfunction and vascular risk assessment (Martin et al., 2013). Furthermore, several studies have reported the role of sTM as a prognostic biomarker in COVID-19 patients (Goshua et al., 2020; Rovas et al., 2020).

4.1. Impact for clinical practice

The elevated biomarkers of endothelial cells, which indicate a manifestation of endothelial dysfunction in COVID-19, might increase the risk of vascular complications, poor outcomes, and death. Laboratory examination of VWF, t-PA, PAI-1, and sTM levels may be useful for vascular risk assessment and predicting adverse outcomes and help guide therapy in COVID-19 patients.

4.2. Limitation

One of the 17 studies included in this meta-analysis was a preprint article. Nevertheless, a thorough assessment has been made to make sure that only sound studies are included. Most of the included studies had a retrospective observational design, and the data were not sufficiently matched or adjusted for confounders. Moreover, our primary endpoints of composite poor outcomes vary widely from ICU admission, severe illness, worsening respiratory status, the need for mechanical ventilation to death. Therefore, the results must be cautiously interpreted.

5. Conclusion

There was an increase in the VWF antigen levels in COVID-19 patients, and the highest levels of VWF antigen were found in deceased COVID-19 patients. Biomarkers of endothelial dysfunction, including VWF antigen, t-PA, PAI-1 antigen, and sTM, are significantly associated with an increased composite poor outcome in patients with COVID-19.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. The corresponding author (A) can be contacted for more information.

CRediT authorship contribution statement

All the authors have participated in literature retrieval, quality assessment of the studies, and viewpoint discussion in this article. A., R. A.N., and Y.A. contributed to writing this article. Y.A. did the statistical analysis. M.J.A. and B.A.M. revised the article. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mvr.2021.104224.

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