

# Temporal changes of hemostatic activity in patients hospitalized for COVID-19: a prospective observational study

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## KEY WORDS

coagulation,  
COVID-19,  
endothelium,  
fibrinolysis,  
respiratory failure

## ABSTRACT

**INTRODUCTION** Hemostatic abnormalities play an important role in the pathogenesis of COVID-19 and are considered determinants of the patients' outcomes. Less is known about the dynamics of these abnormalities in a short-term observation.

**OBJECTIVES** The aim of the study was to evaluate hemostatic activity markers in patients hospitalized for COVID-19 depending on the severity of respiratory failure.

**PATIENTS AND METHODS** This was a prospective observational study enrolling adult patients hospitalized for COVID-19 in a tertiary center in Poland, from January to May 2021. Blood samples were drawn upon admission and 28 days after the admission to measure the markers of coagulation, fibrinolysis, and endothelial dysfunction, and to evaluate whether there are significant differences between these 2 time points. All analyses were performed in the entire cohort and after stratification into 3 groups depending on the degree of respiratory support.

**RESULTS** We recruited 245 patients at the median age of 63 years (interquartile range, 52–69), among whom 158 (64.5%) were men. The analysis of hemostatic markers on admission revealed that hypercoagulability, hypofibrinolysis, and endothelial dysfunction are related to the degree of respiratory support. We found significant differences between the admission and 28-day follow-up in all markers except for plasminogen activity. Interestingly, the markers of endothelial dysfunction remained the highest in the advanced respiratory support group after 28 days, while differences in the other markers diminished.

**CONCLUSIONS** Hemostatic abnormalities are significantly attenuated within a month after a hospital admission due to COVID-19. The initially observed association between severity of the disease and hemostatic derangements persists only for the markers of endotheliopathy.

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**INTRODUCTION** The COVID-19 pandemic was declared by the World Health Organization in 2020 and led to millions of hospitalizations and deaths worldwide.<sup>1</sup> Over time, the growing body of evidence on the disease mechanisms led to the development of effective treatments and vaccines.<sup>2-4</sup> It is now well established that COVID-19 pathophysiology is a complex interplay between inflammation, hemostatic

disturbances, and immunological abnormalities.<sup>5</sup> Clinically, the disease usually presents with respiratory symptoms, frequently leading to respiratory failure and requirement for oxygen therapy, mechanical ventilation, and even extracorporeal oxygenation.<sup>6,7</sup>

One of the characteristic features of COVID-19 is a high prevalence of thromboembolic complications, which encouraged the international

## WHAT'S NEW?

This prospective observational study including 245 patients hospitalized for COVID-19 demonstrates that the degree of hypercoagulability, hypofibrinolysis, and endothelial dysfunction is associated with the requirement for more advanced respiratory support. These abnormalities are significantly attenuated within 28 days since the admission, but intergroup differences persist in the most severely ill patients. This may suggest that endotheliopathy plays a more important role in the pathogenesis of COVID-19 than abnormalities of coagulation and fibrinolysis.

societies to recommend a routine use of thromboprophylaxis in the patients requiring hospitalization for SARS-CoV-2 infection.<sup>8,9</sup> At the same time, basic studies revealed hypercoagulability, hypofibrinolysis, and evidence of endothelial dysfunction in COVID-19 patients.<sup>10-13</sup> The endothelial damage is believed to be a crucial contributor to respiratory failure in the course of COVID-19. It is responsible for intrapulmonary hyperperfusion and impairment of hypoxic vasoconstriction, thus leading to alveolar damage, edema, hemorrhage, and intra-alveolar fibrin deposition in a manner similar to non-COVID-19 acute respiratory distress syndrome.<sup>5</sup> The degree of these abnormalities seems to be related to the severity of the disease.<sup>14,15</sup> Less is known about the temporal changes in hemostatic activity and their patterns in the patients with respiratory failure of a different degree.<sup>16-18</sup>

We conducted this prospective, observational study in the patients hospitalized for COVID-19 to evaluate their hemostatic activity depending on the severity of respiratory failure. Additionally, we aimed to assess the direction and magnitude of changes in coagulation, fibrinolysis, and endothelial function during a short-term observation among COVID-19 survivors.

**PATIENTS AND METHODS** **Design and setting** This was a prospective, observational study including adult patients hospitalized for COVID-19. The recruitment took place at the University Hospital in Kraków, Poland, from January to May 2021. This was a part of the CraCOV-HHS (CRAcow in CoVid pandemics: Home, Hospital and Staff) project, which aimed to develop a model of multidisciplinary inpatient and outpatient care for individuals with SARS-CoV-2 infection. The study protocol was approved by the local bioethics committee (1072.6120.333.2020, December 7, 2020), and complied with the Declaration of Helsinki and its amendments. Detailed information about the design, the recruitment process, and different sub-studies can be found elsewhere.<sup>19</sup>

**Patients** The general inclusion criteria were: 1) informed consent to participate in the study, 2) confirmed SARS-CoV-2 infection (positive reverse transcriptase-polymerase chain reaction or antigen test), and 3) age of at least 18 years. We excluded patients who were unable to give

informed consent to participate in the study and/or were pregnant, and/or had a suspicion of a high-risk pulmonary embolism (sudden cardiac arrest, hemodynamic instability). For each patient we collected detailed demographic and clinical data based on an interview and medical history. Moreover, data on the course of the hospitalization were gathered, including medications, routine laboratory results, and modality of respiratory support.

**Study procedures** **Laboratory tests** Samples of venous blood were drawn from every patient within 24 hours and 28 days after the hospital admission into 3.2% (0.109 mol/l) sodium citrate tubes (1 part of sodium citrate to 9 parts of venous blood), then centrifuged at 2000 × g for 10 minutes within 30 minutes after drawing, and stored in aliquots at -80 °C for further analysis. Additionally, we routinely measured inflammatory markers, that is, procalcitonin and interleukin 6 (Elica, Roche, Meylan, France).

Commercially available immunoenzymatic assays were used to determine plasma tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) antigens (both Hyphen Biomed, Neuville, France), thrombin-antithrombin (TAT) complexes (Enzygnost TAT micro, Siemens, Marburg, Germany), ADAMTS-13 activity and plasmin-antiplasmin (PAP) complexes (both Technoclone, Vienna, Austria). Activity of plasma α2-antiplasmin (α2AP) and plasminogen were measured by chromogenic assays (Berichrom α2-antiplasmin and Berichrom plasminogen; Siemens). Concentrations of D-dimer and von Willebrand factor (vWF) were assessed using a turbidimetric method (Innovance D-dimer and vWF:antigen [Ag]; Siemens). Factor VIII activity was measured using a coagulometric assay with FVIII deficient plasma (Siemens).

Anticardiolipin (aCL), anti-β2-glycoprotein I (aβ<sub>2</sub>GPI), and antiphosphatidylserine-prothrombin (aPS/PT) antibodies of immunoglobulin (Ig) G and IgM isotype were assessed using enzyme-linked immunosorbent assays QUANTA Lite aCL, β2GPI and aPS/PT (Inova Diagnostics, Saint Louis, Missouri, United States) according to the International Society on Thrombosis and Haemostasis guidelines.<sup>20</sup>

**Clot lysis time** Clot lysis time (CLT) was measured as previously described.<sup>21,22</sup> Briefly, citrated plasma was mixed with 15 nM calcium chloride, human thrombin (Merck, Kenilworth, New York, United States) at a final concentration of 0.5 U/ml, 10 μM phospholipid vesicles, and 18 ng/ml of recombinant t-PA (Boehringer Ingelheim, Ingelheim, Germany). The mixture was transferred to a microtiter plate and its turbidity was measured at 405 nm, at 37 °C. CLT was defined as the time from the midpoint of the clear-to-maximum-turbid transition, which represents clot formation, to the midpoint of the maximum-turbid-to-clear transition. Intra-assay and

interassay coefficients of variation were 6% to 8%. The assay was performed in 3 repetitions.

**Subgroup analyses** The patients were stratified according to the severity of respiratory failure using the following criteria:

- 1 No supplemental oxygen group: patients who did not develop respiratory failure in the course of COVID-19 and did not require oxygen therapy;
- 2 Conventional oxygen therapy group: patients who were diagnosed with respiratory failure and required only a conventional oxygen therapy;
- 3 Advanced respiratory support group: patients who developed a severe respiratory failure and required high-flow nasal oxygen therapy and/or noninvasive ventilation and/or invasive mechanical ventilation.

**Statistical analysis** Categorical variables were presented as counts with percentages and compared using the  $\chi^2$  test or the Fisher exact test. Continuous variables were presented as medians with interquartile ranges (IQRs), and compared using the Kruskal–Wallis test. For the comparisons comprising 3 groups, we additionally performed post hoc analyses using the Dunn test. An analysis of paired variables was performed with the Wilcoxon test. We conducted subanalyses of temporal changes in the hemostatic activity stratified by the severity of respiratory failure. This was a complete-case analysis. A *P* value below 0.05 was considered significant. Statistical analyses were performed with R Studio, packages ggplot2 and dplyr (The R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS Study population** The study cohort included 245 patients at the median age of 63 years (IQR, 52–69), among whom 158 (64.5%) were men. The most common comorbidities were hypertension (61.2%), diabetes mellitus (24.9%), and coronary heart disease (17.1%). The patients were divided into the following subgroups: advanced respiratory support group (*n* = 77), conventional oxygen therapy group (*n* = 127), and no supplemental oxygen group (*n* = 41). Detailed description of the entire cohort and comparison of the subgroups are presented in [TABLE 1](#).

**Hemostatic markers on admission and their association with severity of respiratory failure: admission and 28-day follow-up** On admission we observed that the levels of coagulation markers (fibrinogen and TAT) were the highest in the patients requiring advanced respiratory support. Additionally, we observed higher concentrations of fibrinolysis inhibitors ( $\alpha$ 2AP, PAI-1:Ag), fibrinolysis activators (t-PA:Ag), plasminogen, as well as longer CLT in the patients with more severe respiratory failure. Finally, we noted significantly higher levels of the markers of endothelial dysfunction in the patients requiring more advanced respiratory support (PAI-1:Ag, vWF:Ag, and vWF:Ag/ADAMTS-13 ratio).

A similar analysis performed 28 days after the admission to the hospital revealed intergroup differences only in the endothelial dysfunction markers (vWF:Ag and vWF:Ag/ADAMTS-13 ratio).

Detailed results of both analyses, including post hoc tests are presented in [TABLE 2](#).

**Temporal variability of hemostatic activity** The 28-day follow-up evaluation of hemostatic activity was available for 164 patients (66.9%). We revealed a significant decrease in all coagulation, fibrinolysis, and endothelial dysfunction markers, except for plasminogen activity (123.75% vs 121.6%; *P* = 0.94). Particularly large differences were observed for fibrinogen (4.5 vs 3.2 g/l; *P* < 0.001), PAP (1537.6 vs 741.5 ng/ml; *P* < 0.001), PAI-1:Ag (34.1 vs 22.8 ng/ml; *P* < 0.001), and vWF:Ag (300.1% vs 178.2%; *P* < 0.001). This analysis is summarized in [TABLE 3](#) and visualized in [FIGURES 1](#) and [2](#). Additional analyses revealed that similar trends were evident in all subgroups (Supplementary material, [Table S1](#)).

**Antiphospholipid antibodies: intergroup differences and temporal variability** Comparison of antibody levels at admission revealed no significant differences between the studied groups with an exception of  $\alpha\beta_2$ GP1 IgM antibodies, which were lower in the patients not requiring oxygen supplementation than in the conventional oxygen therapy group (2.67 vs 1.94 SMU; *P* = 0.002) and in the advanced respiratory support group (2.52 vs 1.94 SMU; *P* = 0.01), and aPS/PT IgG antibodies, which were higher in the advanced respiratory support group than in the conventional oxygen therapy group (6.92 vs 7.71 IU; *P* = 0.003).

A similar analysis of the 28-day follow-up data showed a higher aCL IgM concentration in the advanced respiratory support and conventional oxygen therapy groups than in the patients without respiratory failure (19.94 vs 17.97 vs 13.43 MPL; *P* = 0.05). Also, aCL IgM concentration was the highest in the advanced respiratory support group, followed by the conventional oxygen therapy group and the no supplemental oxygen group (18.55 vs 11.84 vs 9.58 MPL; *P* < 0.001).

An analysis of temporal changes in antibody concentrations showed an increase in aCL IgG antibodies (5.86 vs 12.55 GPL; *P* < 0.001), aCL IgM antibodies (14.60 vs 17.91 MPL; *P* < 0.001),  $\alpha\beta_2$ GP1 IgG antibodies (2.96 vs 2.59 SGU; *P* < 0.001), and aPS/PT IgG antibodies (7.65 vs 8.66 IU; *P* < 0.001). These results are summarized in [TABLES 2](#) and [3](#). Data on the prevalence of positive antibodies and their changes over time are presented in Supplementary material, [Tables S2](#) and [S3](#).

**DISCUSSION** In this prospective observational study including 245 patients hospitalized for COVID-19, we confirmed a tendency for hypercoagulability, hypofibrinolysis, and endothelial dysfunction at a degree associated with severity of respiratory failure. In all studied groups, the markers of coagulation and fibrinolysis decreased

**TABLE 1** Baseline characteristics of the entire cohort and stratification by the study group

	Overall (n = 245)	Advanced respiratory support (n = 77)	Conventional oxygen therapy (n = 127)	No supplemental oxygen (n = 41)	P value <sup>a</sup>
Baseline demographic and clinical characteristics					
Men, n (%)	158 (64.5)	55 (71.4)	83 (65.4)	20 (48.8)	0.048 <sup>e</sup>
Age, y, median (IQR)	63 (52–69)	63 (53–68)	63 (51.5–69.5)	61 (55–69)	0.99 <sup>c</sup>
Coronary heart disease, n (%)	42 (17.1)	10 (13)	26 (20.5)	6 (14.6)	0.35 <sup>e</sup>
History of myocardial infarction, n (%)	25 (10.2)	8 (10.4)	13 (10.2)	4 (9.8)	0.99 <sup>c</sup>
Chronic heart failure, n (%)	21 (8.6)	6 (7.8)	12 (9.4)	3 (7.3)	0.88 <sup>c</sup>
Atrial fibrillation, n (%)	26 (10.6)	8 (10.4)	13 (10.2)	5 (12.2)	0.94 <sup>c</sup>
History of stroke, n (%)	7 (2.9)	3 (3.9)	3 (2.4)	1 (2.4)	0.80 <sup>c</sup>
Hypertension, n (%)	150 (61.2)	47 (61)	82 (64.6)	21 (51.2)	0.31 <sup>c</sup>
Diabetes mellitus, n (%)	61 (24.9)	24 (31.2)	32 (25.2)	5 (12.2)	0.08 <sup>c</sup>
Peripheral artery disease, n (%)	16 (6.5)	8 (10.4)	6 (4.7)	2 (4.9)	0.25 <sup>c</sup>
Chronic obstructive pulmonary disease, n (%)	9 (3.7)	2 (2.6)	7 (5.5)	0 (0)	0.22 <sup>c</sup>
Asthma, n (%)	25 (10.2)	9 (11.7)	13 (10.2)	3 (7.3)	0.76 <sup>c</sup>
History of VTE, n (%)	13 (5.3)	1 (1.3)	11 (8.7)	1 (2.4)	0.05 <sup>c</sup>
Chronic kidney disease, n (%)	17 (6.9)	6 (7.8)	10 (7.9)	1 (2.4)	0.46 <sup>c</sup>
Hypothyroidism, n (%)	38 (15.5)	11 (14.3)	19 (15)	8 (19.5)	0.73 <sup>c</sup>
Autoimmune disease, n (%)	10 (4.1)	3 (3.9)	5 (3.9)	2 (4.9)	0.96 <sup>c</sup>
Cancer, n (%)	11 (4.5)	5 (6.5)	4 (3.1)	2 (4.9)	0.53 <sup>c</sup>
Laboratory results, median (IQR)					
White blood cells, × 10 <sup>3</sup> /μl	5.85 (4.4–8.3)	7.84 (5.1–9.3)	5.40 (4.3–7.5)	4.98 (4.1–6.8)	0.001 <sup>e,f</sup>
Platelets, × 10 <sup>3</sup> /μl	197 (158–275)	239.5 (164.3–305.3)	187.5 (142.5–258.8)	233 (167.5–267.5)	0.07 <sup>f</sup>
CRP, mg/l	79.2 (38.1–132.8)	123.0 (78.4–165.5)	71.9 (34.7–110.8)	43.4 (11–77.2)	<0.001 <sup>b</sup>
Procalcitonin, ng/ml	0.1 (0.06–0.19)	0.16 (0.11–0.28)	0.09 (0.06–0.16)	0.07 (0.04–0.15)	<0.001 <sup>f</sup>
Interleukin 6, pg/ml	34 (16.7–59.2)	47.2 (22.5–83.8)	34.5 (13.9–58.4)	28.4 (12.2–44.8)	0.018 <sup>e,f</sup>
Maximal LMWH dose					
None, n (%)	2 (0.8)	0 (0)	0 (0)	2 (4.9)	–
Prophylactic, n (%)	86 (35.1)	7 (9.1)	52 (40.9)	27 (65.9)	<0.001 <sup>b</sup>
Intermediate, n (%)	73 (29.8)	21 (27.3)	47 (37)	5 (12.2)	0.008 <sup>e,f</sup>
Therapeutic, n (%)	84 (34.3)	49 (63.6)	28 (22)	7 (17.1)	<0.001 <sup>e,f</sup>

**a** P value for the Kruskal–Wallis test of differences between the groups, post hoc tests were performed using the Dunn test (for qualitative variables); P value for the  $\chi^2$  test of differences between the groups, post hoc analysis was performed using pairwise comparisons (for quantitative variables).

**b** Significant difference between all groups

**c** No significant differences between the groups

**d** Significant difference between no supplemental oxygen and conventional oxygen therapy group

**e** Significant difference between no supplemental oxygen and advanced respiratory support group

**f** Significant difference between conventional oxygen therapy and advanced respiratory support group

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism

within 28 days since initial hospital admission but endothelial dysfunction remained most pronounced in a subgroup of patients with the most severe COVID-19.

The analysis of coagulation markers on admission revealed increased levels of fibrinogen and TAT suggesting marked hypercoagulability. It was accompanied by a significant fibrinolysis shutdown reflected by prolonged CLT. We believe that increased concentrations of potent fibrinolysis inhibitors ( $\alpha$ 2AP and PAI-1)

outweighed elevated levels of tPA and shifted the balance toward hypofibrinolysis.<sup>23,24</sup> Finally, increased vWF:Ag, PAI-1, and particularly high vWF:Ag/ADAMTS-13 ratio suggest significant endothelial dysfunction and significant deviations in the ADAMTS-13–von Willebrand factor axis.<sup>15,25–27</sup> Our results corroborate previous reports in terms of observed abnormalities and confirm their association with severity of COVID-19. The majority of available studies divided patients according to their survival status or requirement



**TABLE 2** Hemostatic markers and antiphospholipid antibody levels on admission and their association with the severity of respiratory failure

Admission					
Parameter	Normal range	Advanced respiratory support (n = 77)	Conventional oxygen therapy (n = 127)	No supplemental oxygen (n = 41)	P value <sup>a</sup>
Fibrinogen, g/l	1.8–3.6	4.9 (4–5.6)	4.3 (3.75–5.1)	4 (3.5–4.6)	<0.001 <sup>b</sup>
Factor VIII, %	50–150	148.7 (109.7–176)	136.7 (106.95–172.45)	139 (101.1–169.6)	0.54 <sup>c</sup>
TAT, µg/l	1.2–4.2	9.69 (7–20.84)	7.09 (5.18–11.3)	7.74 (5.27–14.77)	0.001 <sup>e,f</sup>
CLT, min	74–95 <sup>g</sup>	119 (104–144.5)	110 (100–127)	106 (96–135.25)	0.007 <sup>e,f</sup>
D-Dimer, ng/ml	0–500	1044 (651–2233)	844 (600–1442.5)	845 (615–1559)	0.10 <sup>f</sup>
α2-Antiplasmin, %	80–120	112.3 (104.7–116.3)	108.9 (104.45–115.35)	107.1 (98.1–109.7)	0.01 <sup>d,e</sup>
Plasminogen, %	75–150	126.2 (115.7–137.2)	122.9 (108–133.45)	120.6 (105.4–136.2)	0.17 <sup>f</sup>
t-PA:Ag, ng/ml	4–12	14.38 (11.64–19.09)	13.51 (10.26–16.97)	10.4 (7.34–12.73)	<0.001 <sup>b</sup>
PAI-1:Ag, ng/ml	10–20	38.52 (29.29–47.59)	33.58 (21.66–43.37)	29.23 (22.69–41.07)	0.01 <sup>e,f</sup>
PAP, ng/ml	175–487	1676.3 (1429.6–2200.1)	1577.2 (1352.8–1937.4)	1421.9 (1231–1852.8)	0.008 <sup>d,e</sup>
vWF:Ag, %	50–150	336.7 (289.2–395.2)	317 (257.2–378.65)	244.7 (206.2–295.9)	<0.001 <sup>b</sup>
ADAMTS-13, IU/ml	0.4–1.3	0.84 (0.76–0.9)	0.87 (0.81–0.91)	0.82 (0.73–0.93)	0.17 <sup>c</sup>
vWF:Ag/ADAMTS-13 ratio	– <sup>h</sup>	4.07 (3.52–4.95)	3.65 (3.08–4.48)	3.15 (2.40–4.18)	<0.001 <sup>b</sup>
aCL IgG antibodies, GPL	<15	6.44 (4.19–10.92)	5.85 (4.31–8.98)	6.84 (4.56–9.79)	0.78 <sup>c</sup>
aCL IgM antibodies, MPL	<12.5	14.19 (11.36–19.41)	14.75 (11.73–21.34)	13.63 (10.74–17.94)	0.43 <sup>c</sup>
α <sub>2</sub> GP1 IgG antibodies, SGU	<20	3.13 (2.75–3.97)	2.96 (2.77–3.36)	2.94 (2.76–3.38)	0.47 <sup>c</sup>
α <sub>2</sub> GP1 IgM antibodies, SMU	<20	2.52 (1.75–4.52)	2.67 (1.84–4.52)	1.94 (1.52–2.9)	0.01 <sup>d,e</sup>
aPS/PT IgG, IU	<30	6.92 (5.97–8.45)	7.71 (6.72–9.46)	7.43 (6.36–9.08)	0.02 <sup>f</sup>
aPS/PT IgM, IU	<30	15.23 (9.66–25.01)	15.67 (11.42–23.54)	14.55 (9.59–21.2)	0.76 <sup>c</sup>
28-day follow-up					
Parameter	Normal range	Advanced respiratory support (n = 43)	Conventional oxygen therapy (n = 91)	No supplemental oxygen (n = 30)	P value <sup>a</sup>
Fibrinogen, g/l	1.8–3.6	3.4 (2.9–3.7)	3.2 (2.8–3.6)	3.2 (2.62–3.38)	0.27 <sup>c</sup>
Factor VIII, %	50–150	131.4 (93.75–163.3)	120.8 (87.65–162.45)	116.4 (89.2–151.48)	0.66 <sup>c</sup>
TAT, µg/l	1.2–4.2	4.83 (3.84–7.68)	4.48 (3.67–6.42)	4.56 (3.42–5.86)	0.60 <sup>c</sup>
CLT, min	74–95 <sup>g</sup>	103 (93.5–119)	98 (86–106.75)	99 (91.25–104.5)	0.056 <sup>f</sup>
D-Dimer, ng/ml	0–500	679 (396–1026.5)	644 (405.5–1084)	624 (319.75–1032.25)	0.75 <sup>c</sup>
α2-Antiplasmin, %	80–120	105.8 (101.1–109.7)	104.2 (98.9–108.35)	104.35 (100.67–109.42)	0.29 <sup>c</sup>
Plasminogen, %	75–150	127.1 (118.6–134.85)	119.4 (111.2–129.95)	120 (109.4–133.48)	0.07 <sup>e,f</sup>
t-PA:Ag, ng/ml	4–12	9.08 (6.31–11.64)	8.09 (6.19–9.33)	6.83 (5.42–9.16)	0.13 <sup>e</sup>
PAI-1:Ag, ng/ml	10–20	22.71 (14.45–35.4)	22.36 (14.41–32.96)	22.8 (15.2–30.5)	0.97 <sup>c</sup>
PAP, ng/ml	175–487	754.86 (596.15–1165.24)	732.18 (596.15–1074.32)	732.18 (593.68–933.94)	0.85 <sup>c</sup>
vWF:Ag, %	50–150	205.6 (168.85–252.15)	174.3 (121.65–228.45)	142.6 (112.45–195.08)	0.008 <sup>e,f</sup>
ADAMTS-13, IU/ml	0.4–1.3	0.86 (0.81–0.92)	0.89 (0.83–0.93)	0.88 (0.82–0.94)	0.53 <sup>c</sup>
vWF:Ag/ADAMTS-13 ratio	– <sup>h</sup>	2.33 (1.95–2.91)	1.98 (1.36–2.73)	1.6 (1.33–2.14)	0.01 <sup>e,f</sup>
aCL IgG antibodies, GPL	<15	18.55 (12–33.08)	11.84 (7.32–18.91)	9.58 (6.32–14.07)	<0.001 <sup>b</sup>
aCL IgM antibodies, MPL	<12.5	19.94 (14.62–34.82)	17.97 (13.52–28.82)	13.43 (10.36–20.85)	0.050 <sup>d,e</sup>
α <sub>2</sub> GP1 IgG antibodies, SGU	<20	2.59 (2.3–4.54)	2.65 (2.33–3.34)	2.61 (2.40–2.76)	0.84 <sup>c</sup>
α <sub>2</sub> GP1 IgM antibodies, SMU	<20	2.8 (2.07–4.58)	2.86 (2.12–4.96)	2.12 (1.82–3.35)	0.10 <sup>d</sup>
aPS/PT IgG, IU	<30	8.86 (7.73–10.61)	8.86 (7.06–10.54)	7.93 (6.85–9.67)	0.25 <sup>e</sup>
aPS/PT IgM, IU	<30	15.31 (11.7–19.81)	16.01 (10.88–25.86)	13.79 (8.91–22.65)	0.34 <sup>c</sup>

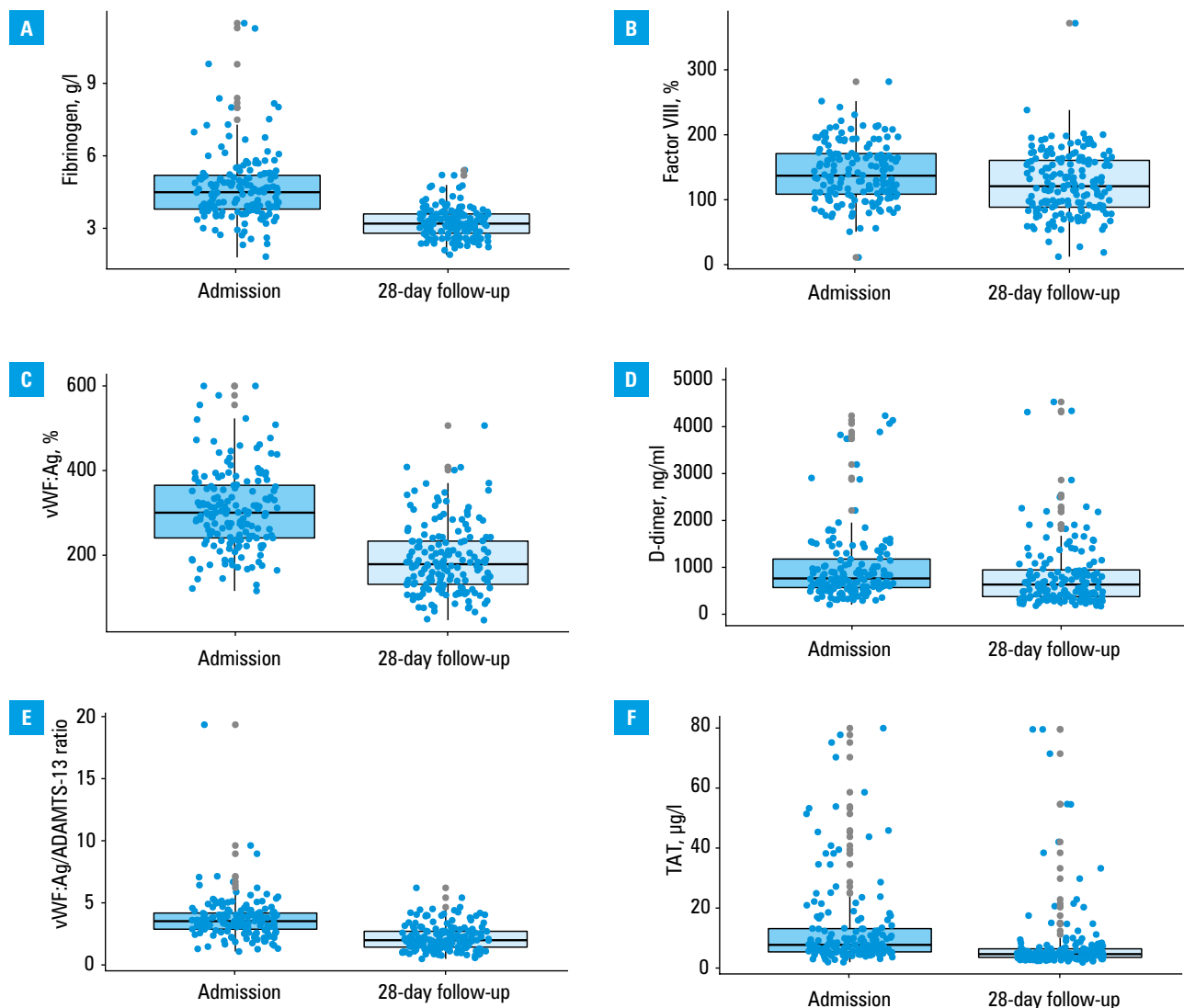
Data are presented as median (interquartile range).

Superscripts **a** to **f**, see **TABLE 1**.

**g** Normal range (lower and upper quartiles) calculated based on the results obtained in 30 sex- and age-matched healthy volunteers

**h** Normal range for vWF:Ag/ADAMTS-13 ratio has not been determined

Abbreviations: aCL, anticardiolipin; aPS/PT, antiphosphatidylserine-prothrombin; β<sub>2</sub>GP1, β-2 glycoprotein I; CLT, clot lysis time; Ig, immunoglobulin; PAI-1, plasminogen activator inhibitor 1; PAP, plasmin-antiplasmin complex; TAT, thrombin-antithrombin complex; t-PA, tissue plasmin activator; vWF:Ag, von Willenbrand factor:antigen

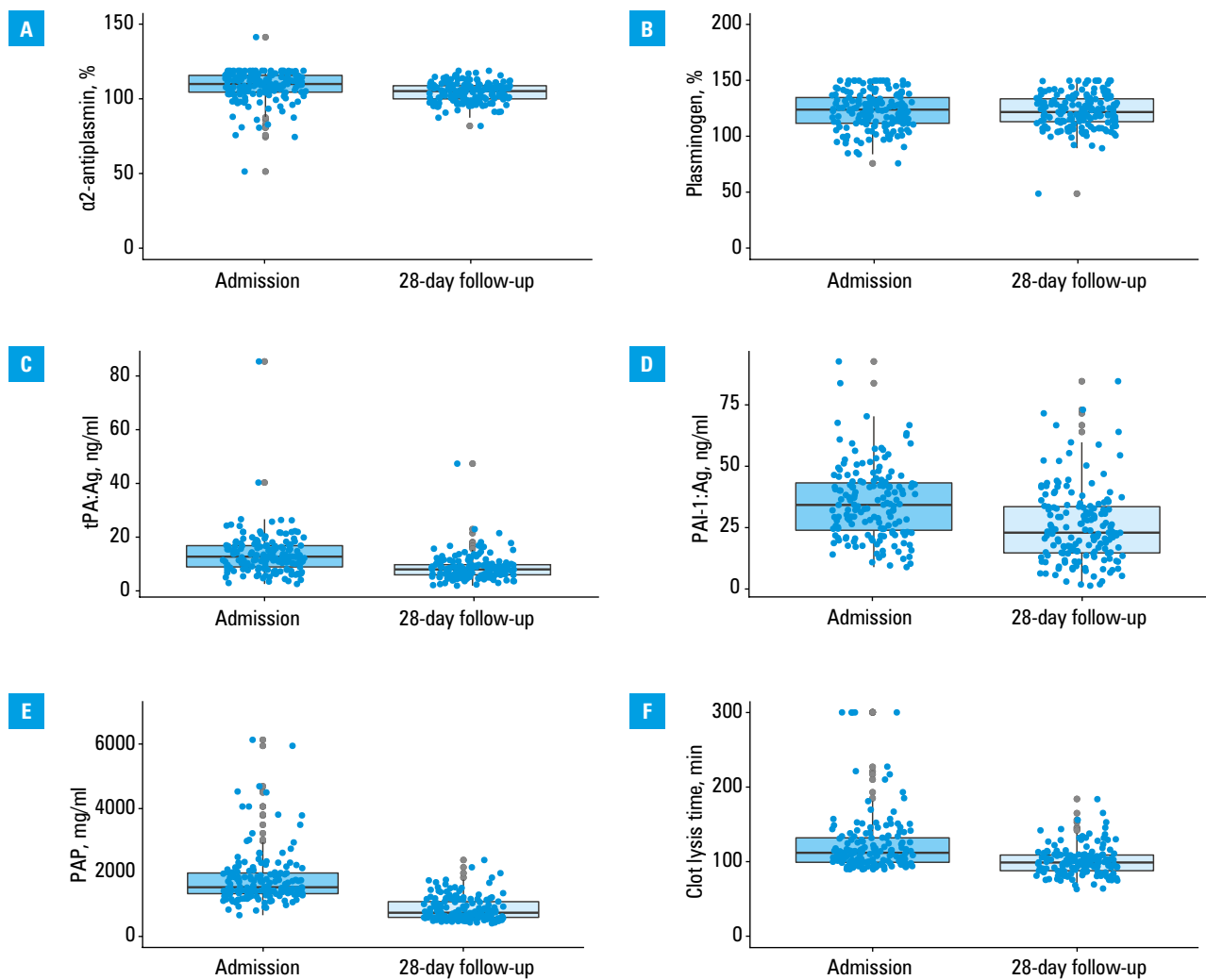


**FIGURE 1** Comparison of coagulation and endothelial parameters between admission and 28-day follow-up. Boxes represent the 25th and 75th percentiles. Whiskers represent minimum (1st quartile –  $1.5 \times$  interquartile range) and maximum (3rd quartile +  $1.5 \times$  interquartile range) values. Dots outside the whiskers represent outliers. Line in the middle of each box represents the median. Abbreviations: see [TABLE 2](#)

for intensive care unit (ICU) admission.<sup>14,28</sup> Our analysis broadens the current knowledge on this issue by using a wider panel of hemostatic markers and by focusing on patients treated primarily in hospital wards and stratified according to the modality of respiratory support. Similar approach was adopted previously by Rauch et al,<sup>29</sup> who reported analogous results but used more common coagulation tests without assessment of fibrinolysis. The hemostatic abnormalities described in patients with COVID-19 made appropriate thromboprophylaxis one of the cornerstones of COVID-19 management. There are also some promising reports showing a potential benefit of fibrinolytic therapy in the patients with severe COVID-19.<sup>30–32</sup>

The requirement for postdischarge thromboprophylaxis remains one of the most widely discussed topics regarding the management of COVID-19 patients. The American Society of Hematology guideline panel discourages it, while some experts suggest considering

extended thromboprophylaxis in the patients with a high risk for thrombotic complications and without a high risk for bleeding.<sup>33,34</sup> On the one hand, the risk of thromboembolic events in patients with COVID-19 is increased up to 4 months after the diagnosis, in comparison with COVID-19–negative controls.<sup>35</sup> On the other hand, a meta-analysis including nearly 19 000 COVID-19 survivors revealed that the absolute incidence of postdischarge venous thromboembolism (VTE) in patients hospitalized for COVID-19 was low and accounted for 1.8%.<sup>36</sup> The currently available literature exploring the impact of COVID-19 on hemostasis after discharge from the hospital pertained to ICU survivors. Serial measurements using viscoelastic assays showed that hypercoagulability and hypofibrinolysis persisted over 6 weeks since admission, but were no longer present in 3-month and 6-month follow-ups.<sup>17,18,37</sup> Our results indicate that the severity of all initially observed abnormalities decreased significantly within 28 days since the admission



**FIGURE 2** Comparison of fibrinolysis parameters between admission and 28-day follow-up. Boxes represent the 25th and 75th percentiles. Whiskers represent minimum (1st quartile – 1.5 × interquartile range) and maximum (3rd quartile + 1.5 × interquartile range) values. Dots outside the whiskers represent outliers. Line in the middle of each box represents the median.

Abbreviations: see [TABLE 2](#)

to the hospital, and such a trend was observed in all subgroups. Another important observation is the disappearance of intergroup differences found upon admission in all assessed markers of coagulation and fibrinolysis. This may suggest that hypercoagulability and hypofibrinolysis are typical for acute phase of the disease and subside relatively quickly. Conversely, the degree of endothelial dysfunction remains the highest in the advanced respiratory support group. This observation, together with the results of Fogarty et al,<sup>38</sup> may indicate a potentially crucial role of endothelial dysfunction in the development of long COVID. Unfortunately, the lack of a healthy control group in our study does not allow for drawing conclusions about normalization of hemostatic parameters in the follow-up. Further studies are required to precisely describe the association of prolonged endotheliopathy with long-term sequelae of COVID-19.

The clinical significance of antiphospholipid antibodies in COVID-19 has been discussed since the first months of the pandemic. The transient presence of aPL antibodies is not an exceptional

feature of COVID-19, and had previously been observed in other viral infections.<sup>39</sup> In previous studies including COVID-19 patients, Lupus anticoagulant was found in 5% to 90% of ICU patients and in 2% to 66% of regular ward patients. The prevalence of other aPL antibodies was characterized by similar variability.<sup>40</sup> However, to date there has been no robust evidence on their pathogenic role in thrombotic events during COVID-19, and data on the association between the level of aPL antibodies and severity of the disease are conflicting.<sup>41–44</sup> Our study shows some differences between the groups in aPS/PT and aβ<sub>2</sub>GP1 IgM antibodies levels. Their magnitude and variable directions suggest that the relation between antiphospholipid antibodies and severity of respiratory failure is rather weak and probably clinically insignificant. This corroborates the results of a meta-analysis by Taha et al,<sup>45</sup> which showed a lack of association between aPL positivity and requirement for invasive mechanical ventilation. Temporal changes in antiphospholipid antibodies profile have not been studied extensively but available studies suggest that the majority of patients with initially positive antibodies

**TABLE 3** Comparison of hemostatic markers and antiphospholipid antibody levels between the admission and 28-day follow-up

Factor	Admission	28-day follow-up	P value <sup>a</sup>
Fibrinogen, g/l	4.5 (3.8–5.2)	3.2 (2.8–3.6)	<0.001
Factor VIII, %	137.35 (108.83–171.42)	121.1 (88.77–161)	<0.001
TAT, µg/l	7.74 (5.42–13.12)	4.68 (3.6–6.44)	<0.001
CLT, min	112 (99.25–132)	99 (88–109)	<0.001
D-Dimer, ng/ml	834.5 (584.25–1473.5)	643.5 (377.75–1083.25)	<0.001
α <sub>2</sub> -Antiplasmin, %	109.95 (104.5–115.73)	105.2 (100–108.8)	<0.001
Plasminogen, %	123.75 (111.57–134.52)	121.6 (112.98–133.38)	0.94
t-PA:Ag, ng/ml	12.84 (9.02–16.94)	8.1 (6.08–9.85)	<0.001
PAI-1:Ag, ng/ml	34.06 (23.73–43.06)	22.76 (14.49–33.36)	<0.001
PAP, ng/ml	1537.58 (1342.16–1991.57)	741.45 (596.15–1086.99)	<0.001
vWF:Ag, %	300.1 (240.33–365)	178.2 (130.57–232.85)	<0.001
ADAMTS-13, IU/ml	0.87 (0.8–0.92)	0.88 (0.82–0.93)	0.003
vWF:Ag/ADAMTS-13 ratio	3.56 (2.91–4.21)	2.02 (1.46–2.74)	<0.001
aCL IgG antibodies, GPL	5.86 (4.26–9.12)	12.55 (8.33–20.9)	<0.001
aCL IgM antibodies, MPL	14.60 (11.54–20.23)	17.91 (12.96–29.03)	<0.001
αβ <sub>2</sub> GP1 IgG antibodies, SGU	2.96 (2.77–3.38)	2.59 (2.33–3.32)	<0.001
αβ <sub>2</sub> GP1 IgM antibodies, SMU	2.47 (1.75–4.4)	2.69 (2.04–4.64)	0.06
aPS/PT IgG	7.65 (6.67–10.02)	8.66 (7.19–10.47)	<0.001
aPS/PT IgM	14.58 (10.80–23.31)	15.31 (10.92–24.01)	0.76

Data are presented as median (interquartile range).

**a** P value for the Wilcoxon test

Abbreviations: see [TABLE 2](#)

have normal levels of antiphospholipid antibodies after 1 to 6 months.<sup>46,47</sup> Our study shows that aCL and aPS/PT levels increase, while αβ<sub>2</sub>GP1 levels decrease within 28 days since the initial admission. Importantly, 1 in 4 patients had at least double-positive antibodies on the 28th day. Unfortunately, we did not gather long-term data on antibody levels, which would definitely offer some valuable insight into the dynamics of the antibody clearance. This information is crucial in terms of establishing an optimal approach to clinical follow-up in the patients with COVID-19 in whom antiphospholipid antibodies were found in the acute phase of the disease. The current recommendations suggest retesting antiphospholipid antibodies-positive patients 12 weeks after the diagnosis, however, this recommendation is based on low-quality data and further research in this area is warranted.<sup>48</sup>

The main strength of this paper is a precise description of the disease course with particular regard to respiratory failure and wide range of tests of hemostatic activity. We are aware of several weaknesses of our study. First, a relatively small study sample as well as relatively low mortality and VTE incidence hindered a precise assessment of associations between these outcomes and hemostatic activity. Second, despite our best efforts, low-molecular-weight heparin was probably administered in some of the enrolled patients before blood samples were collected, which could affect the results. Third, even though we actively endorsed patients to attend the follow-up visit,

the proportion of patients missing in the 28-day follow-up was relatively high. Finally, some might argue that different stratification of patients according to the severity of respiratory failure would be more appropriate, particularly with regard to separation of the patients requiring intubation and hospitalization in the ICU. However, due to a very low number of such patients, after careful discussion among the experts, we decided to include the individuals requiring invasive mechanical ventilation into the advanced respiratory support group.

Summing up, this prospective observational study confirmed that the patients hospitalized for COVID-19 are characterized by hypercoagulability, hypofibrinolysis, and endothelial dysfunction and these abnormalities are related to the severity of respiratory failure. Interestingly, the majority of hemostatic derangements subsided, at least partially, within a month since admission, regardless of the disease course, with an exception of endothelial damage, which was still present at that time. This may suggest that evaluation of hemostasis on admission may be useful in the prediction of the disease severity, and that the observed abnormalities in coagulation and fibrinolysis are limited to the acute phase of the disease. Further studies are required to determine whether persistent endothelial dysfunction and presence of antibodies are associated with long-term thromboembolic complications.



## SUPPLEMENTARY MATERIAL

Supplementary material is available at [www.mp.pl/paim](http://www.mp.pl/paim)

## ARTICLE INFORMATION

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## REFERENCES

- 1 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020; 382: 727-733. [↗](#)
- 2 Watson OJ, Barnsley G, Toor J, et al. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis.* 2022; 22: 1293-1302. [↗](#)
- 3 Shankar-Hari M, Vale CL, et al; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA.* 2021; 326: 499-518.
- 4 Sterne JAC, Murthy S, et al; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA.* 2020; 324:1330-1341. [↗](#)
- 5 Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med.* 2021; 9: 622-642. [↗](#)
- 6 Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med.* 2020; 382: 2372-2374. [↗](#)
- 7 Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020; 382: 1708-1720. [↗](#)
- 8 Cuker A, Tseng EK, Nieuwlaar R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv.* 2021; 5: 872-888.
- 9 Klok FA, Kruij MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020; 191: 145-147. [↗](#)
- 10 Meizoso JP, Moore HB, Moore EE. Fibrinolysis shutdown in COVID-19: clinical manifestations, molecular mechanisms, and therapeutic implications. *J Am Coll Surg.* 2021; 232: 995-1003. [↗](#)
- 11 Kichloo A, Dettloff K, Aljadah M, et al. COVID-19 and hypercoagulability: a review. *Clin Appl Thromb.* 2020; 26: 1076029620962853. [↗](#)
- 12 Gorog DA, Storey RF, Gurbel PA, 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.* 2022; 19: 475-495. [↗](#)
- 13 Onishi T, Shimonishi N, Takeyama M, et al. The balance of comprehensive coagulation and fibrinolytic potential in patients with moderate to severe COVID-19. *Int J Hematol.* 2022; 115: 826-837. [↗](#)
- 14 Len P, Iskakova G, Sautbayeva Z, et al. Meta-analysis and systematic review of coagulation disbalances in COVID-19: 41 studies and 17 601 patients. *Front Cardiovasc Med.* 2022; 9: 794092. [↗](#)
- 15 Corey KM, Olson LB, Naqvi IA, et al. Suppression of fibrinolysis and hypercoagulability, severity of hypoxemia, and mortality in COVID-19 patients: a retrospective cohort study. *Anesthesiology.* 2022; 137: 67-78. [↗](#)

- 16 von Meijenfeldt FA, Havervall S, Adelmeijer J, et al. Sustained prothrombotic changes in COVID-19 patients 4 months after hospital discharge. *Blood Adv.* 2021; 5: 756-759. [↗](#)
- 17 Hulshof A-M, Braeken DCW, Ghossein-Doha C, et al. Hemostasis and fibrinolysis in COVID-19 survivors 6 months after intensive care unit discharge. *Res Pract Thromb Haemost.* 2021; 5: e12579. [↗](#)
- 18 Hulshof A-M, Brüggemann RAG, Mulder MMG, et al. Serial EXTEM, FIBTEM, and tPA rotational thromboelastometry observations in the Maastricht intensive care COVID Cohort—persistence of hypercoagulability and hypofibrinolysis despite anticoagulation. *Front Cardiovasc Med.* 2021; 8: 654174. [↗](#)
- 19 Sydor W, Wizner B, Strach M, et al. CRACoV-HHS: an interdisciplinary project for multi-specialist hospital and non-hospital care for patients with SARS-CoV-2 infection as well hospital staff assessment for infection exposure. *Folia Med Cracov.* 2021; 61: 5-44.
- 20 Devreese KMJ, Ortel TL, Pengo V, et al. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. *J Thromb Haemost.* 2018; 16: 809-813. [↗](#)
- 21 Iwaniec T, Celińska-Löwenhoff M, Zaręba L, et al. Chronic prothrombotic tendency in patients with granulomatosis with polyangiitis. *Pol Arch Intern Med.* 2021; 131: 666-672. [↗](#)
- 22 Pieters M, Philippou H, Undas A, et al. An international study on the feasibility of a standardized combined plasma clot turbidity and lysis assay: communication from the SSC of the ISTH. *J Thromb Haemost.* 2018; 16: 1007-1012. [↗](#)
- 23 Boknäs N, Laine C, Hillarp A, et al. Associations between hemostatic markers and mortality in COVID-19 - compounding effects of D-dimer, anti-thrombin and PAP complex. *Thromb Res.* 2022; 213: 97-104. [↗](#)
- 24 Whyte CS, Simpson M, Morrow GB, et al. The suboptimal fibrinolytic response in COVID-19 is dictated by high PAI-1. *J Thromb Haemost.* 2022; 20: 2394-2406. [↗](#)
- 25 Joly BS, Darmon M, Dekimpe C, 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 Haemost.* 2021; 19: 2193-2198. [↗](#)
- 26 Prasannan N, Heightman M, Hillman T, et al. Impaired exercise capacity in post-COVID-19 syndrome: the role of VWF-ADAMTS13 axis. *Blood Adv.* 2022; 6: 4041-4048. [↗](#)
- 27 Wójcik K, Bazan-Socha S, Celejewska-Wójcik N, et al. Decreased protein C activity, lower ADAMTS13 antigen and free protein S levels accompanied by unchanged thrombin generation potential in hospitalized COVID-19 patients. *Thromb Res.* 2023; 223: 80-86. [↗](#)
- 28 Mancini L, Baronciani L, Artoni A, et al. The ADAMTS13-von Willebrand factor axis in COVID-19 patients. *J Thromb Haemost.* 2021; 19: 513-521. [↗](#)
- 29 Rauch A, Labreuche J, Lassalle F, et al. Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19. *J Thromb Haemost.* 2020; 18: 2942-2953. [↗](#)
- 30 Barrett CD, Moore HB, Moore EE, et al. Fibrinolytic therapy for refractory COVID-19 acute respiratory distress syndrome: scientific rationale and review. *Res Pract Thromb Haemost.* 2020; 4: 524-531. [↗](#)
- 31 Barrett CD, Moore HB, Moore EE, et al. Study of alteplase for respiratory failure in SARS-CoV-2 COVID-19: a Vanguard multicenter, rapidly adaptive, pragmatic, randomized controlled trial. *Chest.* 2022; 161: 710-727.
- 32 Kovács EH, Dembrovsky F, Ocskay K, et al. Effectiveness and safety of fibrinolytic therapy in critically ill patients with COVID-19 with ARDS: protocol for a prospective meta-analysis. *BMJ Open.* 2022; 12: e063855. [↗](#)
- 33 Cuker A, Tseng EK, Nieuwlaar R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: July 2021 update on postdischarge thromboprophylaxis. *Blood Adv.* 2022; 6: 664-671.
- 34 Cuker A, Peyvandi F. COVID-19: Hypercoagulability. <https://www.up-todate.com/contents/covid-19-hypercoagulability>. Accessed Feb 13, 2023.
- 35 Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19: nationwide self-controlled cases series and matched cohort study. *BMJ.* 2022; 377: e069590. [↗](#)
- 36 Zuin M, Engelen MM, Barco S, et al. Incidence of venous thromboembolic events in COVID-19 patients after hospital discharge: a systematic review and meta-analysis. *Thromb Res.* 2022; 209: 94-98. [↗](#)
- 37 Magomedov A, Zickler D, Karaivanov S, et al. Viscoelastic testing reveals normalization of the coagulation profile 12 weeks after severe COVID-19. *Sci Rep.* 2021; 11: 13325. [↗](#)
- 38 Fogarty H, Townsend L, Morrin H, et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. *J Thromb Haemost.* 2021; 19: 2546-2553. [↗](#)
- 39 Abdel-Wahab N, Talathi S, Lopez-Olivo MA, et al. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. *Lupus.* 2017; 27: 572-583. [↗](#)
- 40 Foret T, Dufrost V, Salomon Du Mont L, et al. Systematic review of antiphospholipid antibodies in COVID-19 patients: culprits or bystanders? *Curr Rheumatol Rep.* 2021; 23: 65. [↗](#)
- 41 Hasan Ali O, Bomze D, Risch L, et al. Severe coronavirus disease 2019 (COVID-19) is associated with elevated serum immunoglobulin (Ig) A and antiphospholipid IgA antibodies. *Clin Infect Dis.* 2021; 73: e2869-e2874. [↗](#)

- 42 Najim M, Rahhal A, Khir F, et al. Prevalence and clinical significance of antiphospholipid antibodies in patients with coronavirus disease 2019 admitted to intensive care units: a prospective observational study. *Rheumatol Int.* 2021; 41: 1243-1252. [↗](#)
- 43 Gendron N, Dragon-Durey M-A, Chocron R, et al. Lupus anticoagulant single positivity during the acute phase of COVID-19 is not associated with venous thromboembolism or in-hospital mortality. *Arthritis Rheumatol.* 2021; 73: 1976-1985. [↗](#)
- 44 Favaloro EJ, Henry BM, Lippi G. COVID-19 and antiphospholipid antibodies: time for a reality check? *Semin Thromb Hemost.* 2021; 48: 72-92. [↗](#)
- 45 Taha M, Samavati L. Antiphospholipid antibodies in COVID-19: a meta-analysis and systematic review. *RMD Open.* 2021; 7: e001580. [↗](#)
- 46 Vollmer O, Tacquard C, Dieudonné Y, et al. Follow-up of COVID-19 patients: LA is transient but other aPLs are persistent. *Autoimmun Rev.* 2021; 20: 102822. [↗](#)
- 47 Devreese KMJ, Linskens EA, Benoit D, et al. Antiphospholipid antibodies in patients with COVID-19: a relevant observation? *J Thromb Haemost.* 2020; 18: 2191-2201. [↗](#)
- 48 Wang X, Gkrouzman E, Andrade DCO, et al. COVID-19 and antiphospholipid antibodies: a position statement and management guidance from Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION). *Lupus.* 2021; 30: 2276-2285. [↗](#)