Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

ADAMTS13 activity, von Willebrand factor, factor VIII and D-dimers in COVID-19 inpatients

Emmental Hospital, situated in the rural town of Burgdorf in Switzerland, has treated a low volume of inpatients with COVID-19. Of the 13 admissions prior to 30th April 2020, 4 required treatment in the intensive care unit (ICU). Here we report on 3 consecutive inpatients with severe COVID-19, following the unexpected death of our first patient with severe COVID-19 from pulmonary embolism.

Following our previous findings of massively elevated von Willebrand factor (VWF) and factor VIII clotting activity (FVIII:C) in COVID-19 [1], we complemented our analyses of VWF, FVIII:C and D-dimers during follow-up and included the assay of ADAMTS13 activity using the modified FRETS-VWF73 assay [2].

In the previously published patient, who required intensive care including renal replacement therapy for pneumonia with multiple organ dysfunction [1], there was a slight decrease of VWF antigen, VWF activity and FVIII:C (Table 1, patient 1) after one week of intravenous therapeutic-dose anticoagulation with unfractionated heparin with an anti-FXa-activity target range of 0.6–0.8 U/mL. At this time, we measured a normal ADAMTS13 activity. This patient, 8 weeks after the onset of symptoms, has now been discharged for further rehabilitation while under continued therapeutic anticoagulation with apixaban 2 × 5 mg daily.

We observed a second patient with severe COVID-19 and typical radiological findings of bilateral pneumonia, requiring intensive care with intubation and positive pressure ventilation. She was a 60-year-old female with no previous medical history and no regular medication. Eleven days after the onset of a dry cough, with loss of appetite and a worsening general condition, but with no fever or dyspnoea, she suffered a syncope and was hospitalised. Her haemostatic laboratory values at admission (day 11) and 7 days later are summarised in Table 1 (patient 2). VWF activity, VWF antigen and FVIII:C were markedly elevated, and ADAMTS13 activity was normal. In accordance with our local guidelines for anticoagulation in patients with COVID-19, stratified by D-dimer levels, the patient received a double-prophylactic dose of low molecular weight heparin, i.e. 2 × 5000 IU of dalteparin s.c. per day upon admission. Seven days later, due to increasing D-dimers, anticoagulation was intensified to a therapeutic dose of dalteparin, i.e. 10′000 IU in the morning and 7′500 IU at night. The patient has since recovered and after a 15-day hospitalisation was discharged home with therapeutic anticoagulation with apixaban, 5 mg twice daily. Of note, anti-phospholipid antibodies were normal or near normal (Table 1).

The third patient was a 66-year-old obese female with a medical history of diabetes mellitus type 2, hypertension and hyperlipidaemia, and her daily medication was acetylsalicylic acid 100 mg, candesartan 32 mg, hydrochlorothiazide 25 mg, metformin 2000 mg, vildagliptin 100 mg, fenofibrate 200 mg and pravastatin 40 mg. She was admitted for inpatient monitoring 4 days after the onset of fever of 39.8 °C, a productive cough with white sputum, no dyspnoea but loss of appetite, adynamia and diarrhoea 2 days before admission. Radiological findings showed typical COVID-19 associated diffuse bilateral airspace opacities. Initially her D-dimer levels were 0.53 mg/L and prophylactic dalteparin 5000 IU s.c. once daily was given. While clinically stable and with C-reactive protein decreasing from 78 to 16 mg/L, monitoring of the haemostatic laboratory values 14 days after the onset of symptoms showed elevated D-dimers and massively elevated levels of VWF and FVIII:C (Table 1, patient 3). ADAMTS13 activity was normal, and no antiphospholipid antibodies were detected. A therapeutic dose of dalteparin was started, and three days later the patient could be discharged with apixaban 5 mg twice daily.

In all three patients, erythrocyte sedimentation rate was markedly increased and remained substantially elevated (Table 1). Serum protein electrophoresis reflected acute inflammation and immunofixation was inconclusive with possible traces of oligoclonal bands. Quantitative measurements of IgM, IgG and IgA were normal.

Prior to starting therapeutic dose anticoagulation in these 3 patients, we had observed a patient with severe COVID-19 who seemed to have almost recovered and then died suddenly from clinically obvious pulmonary embolism (with acute right heart failure in the clinical examination as well as on emergency echocardiography) while on prophylactic anticoagulation. In addition, reports from China showed a coagulopathy in 50% of the non-survivors and the prognostic value of D-dimers [3,4]. Based on these observations, we adapted our local guidelines with increased dose heparin according to D-dimer levels. After introducing therapeutic-dose anticoagulation into our therapeutic concept, all patients recovered, with rapid clinical improvement but slow and protracted improvement of D-dimers, persistently high VWF and factor VIII:C levels, and, interestingly, also of erythrocyte sedimentation rate. No haemorrhagic complication occurred. Since then, the findings of highly elevated VWF and factor VIII have also been reported in a small Italian and a large French cohort [5,6]. Furthermore, in two recent autopsy series, thromboembolic complications, including thrombi in the small to mid-sized pulmonary arteries were a striking common finding [7,8]. Randomised trials will clarify the utility of anticoagulation in hospitalised patients with COVID-19 (NCT04344756, NCT04345848, NCT04359212, NCT04362085, and NCT04359277), and we await their results to further inform our practice.

In our patients, normal ADAMTS13 activity together with normal platelet counts (Table 1) clearly excludes thrombotic thrombocytopenic purpura. Notably, there were no schistocytes in the blood smears, which does not support a diagnosis of classic thrombotic microangiopathy. Whereas in severe sepsis or septic shock not due to SARS-CoV-2, some 30% of patients had mildly reduced ADAMTS13 activity of 27–50% [9], our 3 COVID-19 patients had normal ADAMTS13 activity suggesting that ADAMTS13 does not play a major pathogenic role in the COVID-19 coagulopathy. Moreover, the normal platelet counts and high fibrinogen levels in all our patients (lowest value 3.48 g/L) clearly rule out classical disseminated intravascular coagulation (DIC) in our patients, in keeping with the low prevalence of DIC (0–2%) in other

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Table 1
Haematological parameters of COVID-19 patients.

Parameter	Normal	Patient 1		Patient 2		Patient 3
		Day 31[a]	Day 38[a]	Day 11[a]	Day 18[a]	Day 14[a]
D-dimer, mg/L	< 0.5	20.63	6.26	1.1	1.74	2.19
ESR, mm/h	0–20	135	125	> 100	65	98
VWF:activity, %	42–168	520	405	374	303	352
VWF:antigen, %	42–136	555	413	329	251	396
FVIII:C, %	55–164	369	332	310	232	432
ADAMTS13 activity, %	> 51	[b]	56	> 100	83	81
ACA IgG, CU	< 20.0	< 2.6	< 2.6	3.9	2.7	< 2.6
ACA IgM, CU	< 20.0	121.9	77.1	26.2	24.1	1.5
Anti-β2-GPI IgG, CU	< 20.0	6.6	< 6.4	< 6.4	< 6.4	< 6.4
Anti-β2-GPI IgM, CU	< 20.0	275.3	174.1	12.7	14.5	< 1.1
Fibrinogen, g/L	2.00–3.93	5.11	5.82	6.45	3.48	4.33
Thrombocytes, 10^9/L	150–370	352	270	315	318	254
C-reactive protein, mg/L	< 5	14.3	7.5	118	5.1	33.6

ESR, erythrocyte sedimentation rate; VWF, von Willebrand factor; FVIII:C, factor VIII clotting activity; ACA, anti-cardiolipin antibody; anti-β2-GPI, anti-β2 glycoprotein I antibodies.
[a] Refers to days after onset of symptoms.
[b] Not measured.

larger cohorts [6,10–12]. Published evidence has shown viral particles in endothelial cells by electron microscopy, and an endotheliitis has been postulated [13]. Considering these findings, the COVID-19 coagulopathy may be a distinct entity of highly prothrombotic alterations and - in light of the persistently and excessively elevated levels of VWF and FVIII - most probably an endothelial disease.

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R. Escher[a], N. Breakey[a,*], B. Lämmle[b,c,d]
[a] *Department of Medicine, Spital Emmental, Burgdorf, Switzerland*
[b] *Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*
[c] *Center for Thrombosis and Hemostasis, University Medical Center Mainz, Germany*
[d] *Haemostasis Research Unit, University College London, London, UK*
E-mail address: neal.breakey@spital-emmental.ch (N. Breakey).

[*] Corresponding author.