
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.

Thrombosis Research 194 (2020) 42–44

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

## A comprehensive assessment of the coagulation profile in critically ill COVID-19 patients

A number of alterations in coagulation parameters have been described in patients with COVID-19-associated pneumonia. This is associated with an exaggerated inflammatory response that can lead to severe complications and acute respiratory distress syndrome (ARDS) [1].

Coagulopathy has been described in up to 50% of severe manifestations of COVID-19, fulfilling the criteria for disseminated intravascular coagulation (DIC) in the majority (> 70%) of patients. Of note, such coagulopathy was observed substantially more often in severe cases. According to Tang et al. [2] D-dimer levels were four times higher in severely affected patients (median 2.12 μg/mL, IQR 0.77–5.27) compared to non-severe patients (median 0.61 μg/mL, IQR 0.35–1.29). Moreover Guan et al. revealed that high D-dimer levels measured at hospital admission may predict the severity of COVID-19 [3]. Laboratory findings indicate a prothrombotic condition in patients with COVID-19 and consecutively developed venous, arterial and micro-thromboses have been reported [4–8]. However, no report has yet been published demonstrating the full range of coagulation parameter alterations in critically ill COVID-19 patients.

We herein describe the full coagulation profile in four male patients (age 42–77 years) with severe and deleterious COVID-19 associated pneumonia from the University Hospital Frankfurt/Main, Germany. While one patient suffered from severe obesity, the remainder of patients were diagnosed with pre-obesity (median BMI 27.0). The youngest patient (42y) did not have any known pre-existing conditions, while the other patients suffered from arterial hypertension. One of the patients was previously diagnosed with diabetes mellitus and one had a history of urothelial cancer. The included patients were admitted to our intensive care unit (ICU) after presenting with typical symptoms of COVID-19 in the emergency department. A chest CT scan on day one after hospitalization showed typical bilateral multiple ground-glass opacities with peripheral lung and subpleural distributions in all patients. Despite immediate initiation of mechanical ventilation and critical care therapy as put forth by Poston et al. [9], patients rapidly suffered from respiratory failure and a refractory hypoxemia followed by early onset of multi-organ-failure. All patients displayed acute renal failure requiring renal replacement therapy and liver injury consistent to the pathophysiology described recently, suggesting renal tubular cells and liver cells as a target of SARS-CoV-2 [10,11]. Because of refractory hypoxemia the youngest patient received veno-venous extracorporeal membrane oxygenation support.

Therapeutic anticoagulation was administered in all patients using unfractionated heparin for achieving an aPTT between 50 and 70 s. Antithrombin was replaced to maintain a level of 80% or greater. No plasma transfusion or coagulation factor supplementation was performed in any patient. Although the patients were lacking severe pre-existing conditions, none of the patients survived.

The measurements were performed on ACL-TOP coagulation analyzers and using original reagents (Werfen, Barcelona, Spain). The activity of ADAMTS-13 and the antigen of PAI were measured with the ELISA of Haemochrom Diagnostica, Essen, Germany.

The measured coagulation profile included parameters indicative of bleeding and thrombosis, with demographic data and parameters on the severity of the disease shown in Table 1.

Consistent with published data, our results confirmed a substantial increase of D-dimers and fibrinogen levels in all patients, reflecting a response of a systemic inflammatory reaction leading to the activation of blood coagulation.

Furthermore, our results revealed an increase in von Willebrand Factor (VWF) and Factor (F) VIII. These alterations may mirror the systemic endothelial damage recently described in COVID-19 by Varga et al. [12], which has previously been reported for classic ARDS, sepsis and various inflammatory diseases [13]. A direct link between the hemostatic function of VWF and inflammation has already been described earlier [14] and the massive release of VWF may be considered as an indicator of vascular dysfunction [15]. Besides its platelet activation properties, VWF promotes leucocyte adhesion to endothelial cells [16] and large or ultra-large VWF (ULVWF) multimers activate the complement cascade [17]. Further, ADAMTS-13 activity was reduced in all patients, which is a common finding in critically ill patients [18]. Of note, the reduction of ADAMTS-13 activity was not observed to reach an activity of below 10%, indicating an absent thrombotic thrombocytopenic purpura (TTP) in the studied patients [19]. Considering the known linear relationship between ADAMTS-13 and VWF, this might explain the observed decrease.

Interestingly, the changes in the various coagulation factors revealed a different and more complex picture. While the activity of FXII and FXIII were reduced in most patients, most likely in response to increased levels of D-dimer and hyperfibrinolysis, the activity of FII and FVII were reduced in two patients, resulting in a prolonged thromboplastin time. A speculative but reasonable explanation for the observed reduction of FII and FVII may result from several underlying conditions such as liver failure, vitamin K deficiency or treatment with antibiotics. The other coagulation factors, FV, FVIII, FIX, were normal or elevated in all patients, suggesting that patients did not present all criteria of DIC in consuming coagulation factors.

In particular, no hereditary thrombophilia was diagnosed and various measurements were negative in regard to antiphospholipid antibodies resulting in no evidence of antiphospholipid syndrome.

A further observation was the reduced levels of protein C and protein S: It has been repeatedly shown that these parameters are associated with a poor outcome of sepsis [20]. A strongly increased plasminogen activator inhibitor 1 (PAI-1) level above the upper limit of detection was observed in 50% of the patients, indicating an increased risk for thromboembolic events.

In conclusion, the coagulation profile in critically ill COVID-19 patients showed a substantial activation of coagulation and fibrinolysis with highly increased levels of D-dimer and VWF as potential markers

https://doi.org/10.1016/j.thromres.2020.06.026
Received 22 April 2020; Received in revised form 15 June 2020; Accepted 16 June 2020
Available online 18 June 2020

**Table 1**
Coagulation profile in critically ill COVID-19 patients.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Reference range |
|---|---|---|---|---|---|
| Age (years) | 77 | 68 | 42 | 68 | |
| BMI | 38.1 | 26.1 | 26.1 | 27.8 | |
| Day of illness | 4 | 5 | 4 | 4 | |
| SOFA score | 12 | 11 | 12 | 11 | |
| Thromboplastin time (%) | 65 | 88 | 47 | 88 | 70–130 |
| aPTT (s) | 37 | 62 | 69 | 51 | 25–37 |
| Fibrinogen (mg/dL) | 741 | 380 | 639 | 707 | 190–498 |
| Antithrombin-activity (%) | 49 | 54 | 101 | 51 | 80–128 |
| D-dimer (ng/mL) | 3315 | 12,639 | 13,221 | 4159 | < 500 |
| Platelets ($10^3$/μL) | 391 | 172 | 251 | 174 | 146–328 |
| Factor II (%) | 61.7 | 47.6 | 51.4 | 65.7 | 75–129 |
| Factor V (%) | 98.2 | 96 | 121.4 | 163.4 | 80–148 |
| Factor VII (%) | 57.1 | 73.7 | 24.2 | 68.4 | 48–148 |
| Factor VIII (%) | 339.6 | 73.7 | 261.8 | 339.5 | 48–139 |
| Factor IX (%) | 150.8 | 106.1 | 130 | 97 | 68–133 |
| Factor XI (%) | 64 | 51 | 60 | 82 | 69–144 |
| Factor XII (%) | 34.8 | 29.8 | 32.1 | 47.4 | 66–146 |
| Factor XIII (%) | 120.9 | 39 | 58.8 | 46.3 | 70–155 |
| v. Willebrand antigen (%) | > 600 | > 600 | > 600 | 536 | 60–150 |
| Protein C-activity (%) | 53 | 59 | 87 | 65 | > 72 |
| Free protein S-antigen (%) | 55 | 48 | 45 | 37 | 68–116 |
| DRVVT screen (s) | 53.8 | 42.6 | 54.7 | 49.6 | 28.4–45.8 |
| DRVVT ratio | 1.19 | 1.20 | 1.19 | 1.22 | 0.93–1.40 |
| Lupus sensitive PTT (s) | 35.9 | 35.4 | 58.1 | 33.6 | 23.1–38.4 |
| Anti-cardiolipin IgM (U/mL) | 2.7 | 10.3 | < 1.0 | 1.7 | < 20 |
| Anti-cardiolipin IgG (U/mL) | 6.7 | 3.9 | 4 | 6.4 | < 20 |
| Anti-ß2-glykoprotein IgM (U/mL) | 1.7 | 1.1 | < 1.1 | < 1.1 | < 20 |
| Anti-ß2-glykoprotein IgG (U/mL) | < 6.4 | 7.7 | < 6.4 | < 6.4 | < 20 |
| ADAMTS-13 (%) activity | 36 | 19 | 36 | 28 | 40–130 |
| PAI-Ag (ng/mL) | 36.2 | > 62.4 | 10.9 | > 62.4 | 7–43 |
| Factor V-mutation | Wild type | Wild type | Wild type | Wild type | |
| Factor II-mutation | Wild type | Wild type | Wild type | Wild type | |

BMI: body-mass-index; SOFA score: sepsis-related organ failure assessment score; aPTT: activated partial thromboplastin time; DRVVT: diluted-Russel-Viper-Venom-Test; PAI: plasminogen activator inhibitor; AT levels are pre-substitution values.

of endothelial dysfunction. No clinical signs and no laboratory alterations indicative for bleeding or findings associated with DIC (e.g. altered platelet counts or fibrinogen levels) have been detected.

## Author contributions

EHA, KZ and WM analyzed the data and wrote the text.

## Declaration of competing interest

There are no conflicts of interests.

## References


[1] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet. 395 (2020) 507–513, https://doi.org/10.1016/s0140-6736(20)30211-7.

[2] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, Journal of Thrombosis and Haemostasis. 18 (5) (2020) 1094–1099.

[3] W.-j. Guan, Z.-y. Ni, Y. Hu, W.-h. Liang, C.-q. Ou, J.-x. He, L. Liu, H. Shan, C.-l. Lei, D.S. Hui, Clinical characteristics of coronavirus disease 2019 in China, New England Journal of Medicine 382 (18) (2020) 1708–1720.

[4] J. Xu, L. Wang, L. Zhao, F. Li, J. Liu, L. Zhang, Q. Li, J. Gu, S. Liang, Q. Zhao, Risk assessment of venous thromboembolism and bleeding in COVID-19 patients, (2020).

[5] J. Chen, X. Wang, S. Zhang, B. Liu, X. Wu, Y. Wang, X. Wang, M. Yang, J. Sun, Y. Xie, Findings of acute pulmonary embolism in COVID-19 patients, (2020) (Available at SSRN 3548771).

[6] S. Cui, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, Journal of Thrombosis and Haemostasis 18 (6) (2020) 1421–1424.

[7] F. Klok, M. Kruip, N. van der Meer, M. Arbous, D. Gommers, K. Kant, F. Kaptein, J. van Paassen, M. Stals, M. Huisman, Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thrombosis Research. 191 (2020) 145–147.

[8] S.E. Fox, A. Akmatbekov, J.L. Harbert, G. Li, J.Q. Brown, R.S. Vander Heide, Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series From New Orleans, medRxiv, 2020.

[9] J.T. Poston, B.K. Patel, A.M. Davis, Management of critically ill adults with COVID-19, Jama. (2020), https://doi.org/10.1001/jama.2020.4914.

[10] S. Naicker, C.-W. Yang, S.-J. Hwang, B.-C. Liu, J.-H. Chen, V. Jha, The Novel Coronavirus 2019 epidemic and kidneys, Kidney International. 97 (5) (2020) 824–828.

[11] C. Zhang, L. Shi, F.-S. Wang, Liver injury in COVID-19: management and challenges, The Lancet Gastroenterology & Hepatology. 5 (5) (2020) 428–430.

[12] Z. Varga, A.J. Flammer, P. Steiger, M. Haberecker, R. Andermatt, A.S. Zinkernagel, M.R. Mehra, R.A. Schuepbach, F. Ruschitzka, H. Moch, Endothelial cell infection and endotheliitis in COVID-19, The Lancet. (2020), https://doi.org/10.1016/S0140-6736(20)30937-5.

[13] J.E. Whitney, B. Zhang, N. Koterba, F. Chen, J. Bush, K. Graham, S.F. Lacey, J.J. Melenhorst, D.T. Teachey, J.L. Mensinger, Systemic endothelial activation is associated with early acute respiratory distress syndrome in children with extra-pulmonary sepsis, Critical Care Medicine. 48 (2020) 344–352.

[14] C. Kawecki, P. Lenting, C. Denis, von Willebrand factor and inflammation, Journal of Thrombosis and Haemostasis. 15 (2017) 1285–1294.

[15] B. Petri, A. Broermann, H. Li, A.G. Khandoga, A. Zarbock, F. Krombach, T. Goerge, S.W. Schneider, C. Jones, B. Nieswandt, von Willebrand factor promotes leukocyte

extravasation, Blood, The Journal of the American Society of Hematology. 116 (2010) 4712–4719.
[16] V. Huck, M.F. Schneider, C. Gorzelanny, S.W. Schneider, The various states of von Willebrand factor and their function in physiology and pathophysiology, Thrombosis and Haemostasis. 111 (2014) 598–609.
[17] S. Feng, X. Liang, M.H. Kroll, D.W. Chung, V. Afshar-Kharghan, von Willebrand factor is a cofactor in complement regulation, Blood, The Journal of the American Society of Hematology. 125 (2015) 1034–1037.
[18] J. Aibar, P. Castro, G. Espinosa, S. Fernandez, C. Hernandez, M. Rinaudo, M. Butjosa, D. Tassies, J.C. Reverter, J.M. Nicolas, ADAMTS-13 in critically ill patients with septic syndromes and noninfectious systemic inflammatory response syndrome, Shock. 43 (2015) 556–562, https://doi.org/10.1097/shk.0000000000000341.
[19] S.K. Vesely, J.N. George, B. Lämmle, J.-D. Studt, L. Alberio, M.A. El-Harake, G.E. Raskob, ADAMTS13 activity in thrombotic thrombocytopenic purpura–hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients, Blood. 102 (2003) 60–68.
[20] S. Larosa, S. Opal, B. Utterback, B. Yan, J. Helterbrand, A. Simpson, N. White, C. Fisher, Decreased protein C, protein S and antithrombin III levels are predictive of poor outcome in gram-negative sepsis caused by Burkholderia pseudomallei, Critical Care: BioMed Central (2000) P30.

E.H. Adam, K. Zacharowski, W. Miesbach*
*Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Goethe University, Frankfurt, Germany*
*Haemostaseology and Hemophilia Center, Medical Clinic 2, Institute of Transfusion Medicine, University Hospital Frankfurt, Frankfurt, Germany*
*E-mail address:* wolfgang.miesbach@kgu.de (W. Miesbach).

* Corresponding author at: Department of Haemostaseology and Hemophilia Center, Medical Clinic 2, Institute of Transfusion Medicine, University Hospital Frankfurt, Theodor Stern Kai 7, 60596 Frankfurt am Main, Germany.