EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Editorial

How can we better predict pulmonary blood clots in patients hospitalised for COVID-19?

Laurent Bertoletti, Menno V. Huisman

Please cite this article as: Bertoletti L, Huisman MV. How can we better predict pulmonary blood clots in patients hospitalised for COVID-19?. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.03092-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Title : **How can we better predict pulmonary blood clots in patients hospitalized for COVID-19 ?**

Laurent BERTOLETTI[1,2,3,4],

Menno V. HUISMAN[5].

Affiliations:

1. Service de Médecine Vasculaire et Thérapeutique, CHU de St-Etienne, Saint-Etienne, France;
2. INSERM, UMR1059, Equipe Dysfonction Vasculaire et Hémostase, Université Jean-Monnet, F-42055, Saint-Etienne, France ;
3. INSERM, CIC-1408, CHU Saint-Etienne, F-42055, Saint-Etienne, France.
4. F-CRIN INNOVTE network, Saint-Etienne, France.
5. Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

Corresponding author: Menno HUISMAN,

Department of Thrombosis and Hemostasis,

Leiden University Medical Center, Leiden

Albinusdreef 2

2333ZA Leiden The Netherlands

Telephone + 31 71 56 3761

The emergence of COVID-19 has put pressure on health systems around the world[1, 2]. This coronavirus has also questioned much of our medical knowledge, with each day seeing the appearance of a new possible clinical expression of the virus[3]. Although its physiopathology is still poorly understood, the vascular tropism of the disease now seems to be a major pathway[4]. Recent studies highlight the development of a specific pulmonary vascular endothelialitis, associated with thrombosis and angiogenesis[5].

A strong association between coronavirus infection and the risk of venous thromboembolism (VTE) was suggested by Chinese authors[6], who described an increase in the blood level of d-dimer (increase associated with an increased risk of death) [7]. A specific coagulopathy was evoked[8], as well as a possible increased risk of VTE. However, it also appeared that the COVID-19 may also challenge our usual way to deal with VTE suspicion and management[9]. First, the respiratory impairment of COVID-19 directly impacts the usual modalities of suspicion of VTE. In patients admitted to the emergency department with a respiratory picture compatible with a COVID-19, the symptomatology close to that of pulmonary embolism (PE) may hinder the evocation of alternative diagnoses. The (now classic) secondary respiratory deterioration raises the same question of alternative diagnosis as PE. When VTE is suspected, the pandemic situation makes access to vascular and thoracic explorations more complex, requiring the development of parallel flows for contagious and non-contagious patients. In patients admitted to ICU, the issues are even more specific, with the difficulty of diagnosing VTE (and particularly PE) in sedated patients, and the technical difficulty of performing chest imaging in intubated patients with renal failure.

It is in this context in this issue of the Journal Mouhat et al report [REF TO BE INCLUDED], their retrospective analysis concerning the suspicion of pulmonary embolism in COVID patients admitted to a university hospital in a pandemic zone.

The authors analyzed the clinical and biological data of 349 COVID patients admitted in one month. Among the 162 patients who underwent a computed tomography pulmonary angiography (CTPA) because of a severe clinical presentation (respiratory rate ≥ 30/min, SpO2 ≤ 93%, or rapid clinical worsening), a pulmonary embolism was diagnosed in 44 patients (27.2%), of which 1/5th at hospital admission. Two factors were associated with the risk of PE: high D-dimer levels, and lack of anticoagulant therapy. The association between PE and the lack of anticoagulant therapy was mainly supported by the inclusion of all PE patients (including PE diagnosed at admission). The authors propose a d-dimer threshold at 2590 ng/mL to predict CTPA-confirmed PE in severe COVID-19 patients, with high accuracy: AUC of 0.88, (95% CI, 0.809-0.932), $p < 0.001$. Patients with D-dimers above the cut-off of 2590 ng/mL accounted for 36.0% (95% CI, 27.5-45.2) of the overall population, 42.6% (95% CI, 30.7-55.2) of patients in ICU, and 15.9% (95% CI, 9.2-24.9) of patients in conventional COVID wards, respectively. While their study is retrospective and as a result exposed patients to heterogeneous management, it gives us an interesting perspective.

Where do we go from here? First, we need to prospectively assess the frequency of PE at admission and the validation of the D-dimer cut-off of 2500 to indicate PE to be present in COVID-19 patients. The current work suggests that only one in five PE was diagnosed at admission, which is lower than in another study[10], but in agreement with a recent retrospective study[11]. It also confirms that D-dimers still have a role in the stratification of a patient prognosis, being associated

with an increased risk of death (if more than >1000) but also PE (if more than >2500). The combination of D-dimer results with a clinical prediction rule (as the Geneva[12], the Wells[13], or the YEARS scores[14] proposed in the European guidelines[15]) is still under debate and this needs also prospective validation. Secondly, we need to determine factors associated with hospital-acquired VTE in COVID-19 patients. In the current work by Mouhat et al, most of PE occurred after admission. Thromboprophylaxis is indicated in any patient admitted for COVID-19[8], and many authors proposed to increase the dosage of usual parenteral drugs, with the hope to decrease the rate of venous and arterial complications [16]) without increasing the bleeding risk. Hence, the risk and benefits of such modified thromboprophylaxis, as well as the potential of pharmacological agents targeting thromboinflammation[17], deserve further analysis.

Bibliography

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen K-Y, Chen R, Tang C, Wang T, Chen P, Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* 2020; : 1–13.

2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* Elsevier Ltd; 2020; 395: 1054–1062.

3. McGonagle D, O'Donnell J, Sharif K, Emery P, Bridgewood C. Immune Mechanisms of Pulmonary Intravascular Coagulopathy (PIC) in COVID-19 Pneumonia. *Lancet Rheumatol.* Elsevier Ltd; 2020; 2019: 1–9.

4. Gupta A, Madhavan M V., Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat. Med.* Springer US; 2020; 26.

5. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein CMD, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N. Engl. J. Med.* 2020; 383: 120–128.

6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J. Thromb. Haemost.* 2020; .

7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.* 2020; 18: 844–847.

8. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J. Thromb. Haemost.* 2020; n/a: 0–2.

9. Bertoletti L, Couturaud F, Montani D, Parent F, Sanchez O. Venous thromboembolism and Covid-19. *Respir. Med. Res.* 2020; : 100759.

10. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S. Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. *Circulation* 2020; : 1–6.

11. Freund Y, Drogrey M, Miró Ò, Marra A, Féral-Pierssens A, Penaloza A, Lara Hernandez BA, Beaune S, Gorlicki J, Vattinada Ayar P, Truchot J, Pena B, Aguirre A, Fémy F, Javaud N, Chauvin A, Chouihed T, Montassier E, Claret P, Occelli C, Roussel M, Brigant F, Ellouze S, Le Borgne P, Laribi S, Simon T, Lucidarme O, Cachanado M, Bloom B, Goulet H, et al. Association between Pulmonary Embolism and COVID-19 in ED patients Undergoing CTPA: the PEPCOV international retrospective study. *Acad. Emerg. Med.* 2020; : acem.14096.

12. Le Gal G, Righini M, Roy P-M, Sanchez O, Aujesky D, Bounameaux H, Perrier A. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann. Intern. Med.* 2006; 144: 165–171.

13. Anderson DR, Kovacs MJ, Kovacs G, Stiell I, Mitchell M, Khoury V, Dryer J, Ward J, Wells PS. Combined use of clinical assessment and d-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED Study). *J. Thromb. Haemost.* 2003; 1: 645–651.

14. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, Faber LM, Hazelaar GM, Heringhaus C, Hofstee H, Hovens MMC, Kaasjager KAH, van Klink RCJ, Kruip MJHA, Loeffen RF, Mairuhu ATA, Middeldorp S, Nijkeuter M, van der Pol LM, Schol-Gelok S, ten Wolde M, Klok FA, Huisman M V. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017; 6736.

15. Konstantinides S V., Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, Huisman M V., Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Áinle FN, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur. Respir. J.* 2019; 54: 1901647.

16. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb. Res.* Elsevier Ltd; 2020; : 100632.

17. Bikdeli B, Madhavan M V., Gupta A, Jimenez D, Burton JR, Der Nigoghossian C, Chuich T, Nouri SN, Dreyfus I, Driggin E, Sethi S, Sehgal K, Chatterjee S, Ageno W, Madjid M, Guo Y, Tang L V., Hu Y, Bertoletti L, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Tafur AJ, Francese DP, Batra J, et al. Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research. *Thromb. Haemost.* 2020; 120: 1004–1024.