EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Prevalence of pulmonary embolism in patients with COVID 19 at the time of hospital admission

Mitja Jevnikar, Olivier Sanchez, Richard Chocron, Marc Andronikof, Maurice Raphael, Olivier Meyrignac, Laure Fournier, David Montani, Benjamin Planquette, Mary Soudani, Athénaïs Boucly, Jeremie Pichon, Mariana Preda, Antoine Beurnier, Sophie Bulifon, Andrei Seferian, Xavier Jaïs, Olivier Sitbon, Laurent Savale, Marc Humbert, Florence Parent

Please cite this article as: Jevnikar M, Sanchez O, Chocron R, *et al*. Prevalence of pulmonary embolism in patients with COVID 19 at the time of hospital admission. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00116-2021).

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.

Copyright ©The authors 2021. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Prevalence of pulmonary embolism in patients with COVID 19 at the time of hospital admission.

Mitja Jevnikar, MD[1,2,3], Olivier Sanchez, MD, PhD[4,5,6], Richard Chocron, MD, Ph[6,7], Marc Andronikof[1,8] MD, Maurice Raphael, MD[1,9], Olivier Meyrignac MD, PhD[1,10], Laure Fournier, MD, PhD[6,11], David Montani, MD, PhD[1,2,3], Benjamin Planquette, MD, PhD[4,5,6], Mary Soudani, MD[1,12], Athénaïs Boucly MD[1,2,3], Jeremie Pichon, MD[1,2,3], Mariana Preda, MD[1,2,3], Antoine Beurnier, MD[1,2,13], Sophie Bulifon, MD[1,2,3], Andrei Seferian, MD[1,2,3], Xavier Jaïs, MD[1,2,3], Olivier Sitbon MD, PhD[1,2,3], Laurent Savale, MD[1,2,3], Marc Humbert MD, PhD[1,2,3], Florence Parent MD[1,2,3]

1. Université Paris-Saclay, Faculty of Medicine, Le Kremlin-Bicêtre, France

2. INSERM UMR_S 999, Le Kremlin-Bicêtre, France

3. AP-HP, Service de Pneumologie et soins intensifs respiratoires, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

4. AP-HP, Service de Pneumologie et Soins Intensifs, Hôpital Européen Georges Pompidou, Paris, France

5. INSERM UMR-S 1140; Paris, France and INNOVTE, St-Etienne, France.

6. Université Paris Descartes, Faculty of Medicine, Paris, France

7. AP-HP, Service d'Urgence, Hôpital Européen Georges Pompidou, Paris, France

8. AP-HP, Service d'Urgenc, Hôpital Antoine Béclère, Clamart, France.

9. AP-HP, Service d'Urgence, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

10. AP-HP, Service de Radiologie, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

11. AP-HP, Service de Radiologie, Hôpital Européen Georges Pompidou, Paris, France

12. AP-HP, Department de Gériatrie, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

13. AP-HP, Service de physiologie et d'explorations fonctionnelles respiratoires

(CRISALIS/F-CRIN network), Hôpital Bicêtre, Le Kremlin-Bicêtre, France

Correspondance:

Florence Parent, MD

Service de pneumologie, Le Kremlin-Bicêtre, France

78 rue du général Leclerc, 94270 Le Kremlin Bicêtre, France.

Tél: +33 145 21 78 76

Fax: +33 145 21 79 71

Email: florence.parent@aphp.fr

A high prevalence of venous thromboembolism (VTE) has been reported during Intensive Care Unit (ICU) hospitalisation in patients with severe coronavirus disease (COVID-19)[1,2]. In most cases, the diagnosis of pulmonary embolism (PE) was incidental as patients underwent computed tomography pulmonary angiography (CTPA) for aggravation of their respiratory condition. Higher mortality is also described in patients with high D-Dimer levels suggesting that VTE complication may contribute to unfavourable prognosis[3,4]. Even though, prevalence of thromboembolic complications during ICU hospitalisation seems to be high, the prevalence of PE at hospital admission for COVID-19 is unknown and may be underestimated.

In the present research letter, we report a prospective multicentre study that evaluates the PE prevalence in patients admitted for COVID-19, at the time of admission in three tertiary hospitals, Bicêtre Hospital and Béclère Hospital, University Paris-Saclay, and European Georges Pompidou Hospital, Paris University.

All consecutive adult outpatients hospitalized between April 15, 2020 to May 23, 2020 with a diagnosis of COVID-19 were included and underwent a CTPA, if not contraindicated, at the time of hospital admission. Patients with renal failure (<30mL/min of clearance) or contraindications to iodinated contrast material were excluded from the study. COVID-19 diagnosis was confirmed by the presence of positive SARS-CoV-2 RT-PCR and/or typical CT abnormalities (i.e ground-glass opacities and/or consolidation in the lung periphery)[5,6]. Hospital admission was decided by the clinician in charge at the emergency department (ED) of each participating hospital according to clinical criteria.

The CT patterns of COVID-19 pneumonia and the presence of PE were analysed locally by a senior radiologist and a pulmonologist. Patients without PE received prophylactic anticoagulation during hospitalisation, according to local practice.

Patients were prospectively followed-up for three months or until death, by a telephone interview within 3 months after admission.

Performing systematic CTPA was in accordance with the multidisciplinary medical crisis team for COVID-19 and all patients received oral information about data

collection. Upon consent, data were recorded in an anonymous database registered to the National Commission on Informatics and Liberty (n°26750045200441). The study was been approved by the CERAPHP Centre (Comité d'éthique de la recherche APHP Centre; IRB registration: #00011928).

Quantitative data are expressed as median (interquartile range, 25% to 75% [IQR]) and qualitative data are expressed as number of occurrences, n (%). The prevalence of PE was calculated, and the 95% confidence intervals (CI) were determined. Comparisons between groups were performed using the independent student's t-test if the distribution of variables was normal and by the Wilcoxon test if not normally distributed. A multivariable logistic regression model adjusted for age and sex was calculated for significant results ($p<0.05$). Categorical variables were compared using the chi-square test for independence. XLSTAT (Addinsoft, 2019, Long Island, NY, USA) and Graphpad prism (GraphPad Software, La Jolla California, USA) software were used. A p-value of <0.05 was considered statistically significant.

During the study period, 135 consecutives outpatients were hospitalised for COVID-19 at the three participating hospitals. Among them, 29 (21.5%) were excluded from the study, mainly due to contraindications for iodinated contrast administration (n=12), inability to understand oral information (n=7) and screening failure (n=10). Of the 106 included patients, 5 (4.7%) patients were directly admitted to an ICU.

Overall, PE was diagnosed in 15 of 106 patients giving a prevalence of 14.2% (95%CI 7.5-20.8). Among the 5 patients directly admitted in ICU, 1 had a confirmed PE at admission. Table 1 summarises the characteristics of included patients and the chest CT-scan features. CTPA was well tolerated with no aggravation of renal function (n=87; p=0.52) and only one complication (0.9%) was reported due to iodinated material extravasation with no severe consequences.

Patients with confirmed PE on admission had significantly higher D-dimer median concentrations, more often needed oxygen administration in the ED and had longer median time from symptoms to hospital admission as compared to patients without PE. In multivariable analysis, only high D-dimer median concentrations (OR 1.001 [1-1.002]) and time from symptoms to hospital admission (OR 1.103 [1.019-1.193]) were independently associated with PE.

No significant difference was observed for CT staging of COVID-19 lung involvement between patients with and without PE (p=0.85) and 5/15 (33.3%) patients had PE in the same location as COVID-19 pneumonia. PE was lobar in 7 (46.7%), segmental in 6 (40%) and sub-segmental in 2 (13.3%) cases, respectively. Right ventricular/left ventricular diameter ratio > 1 was observed in 5 patients (33.3%).

During the time of hospitalisation, 15/91 (16.5%) patients had a repeated CTPA for clinical worsening without identification of any new PEs. Patients without PE at admission received standard VTE prophylaxis by Enoxaparin 4000UI/Day. In ICU-patients, obese patients (BMI > 35) and patients with high level of biological inflammation (D-Dimer level greater than 1000µg/L) high intensity VTE prophylaxis by Enoxaparin 4000 UI/12h was used (or Enoxaparin 6000UI/12h in case of weight greater than 120 kg). After discharge, standard VTE prophylaxis was prolonged for 2-4 weeks in cases of persistently impaired mobility or persistently high levels of biological inflammation. Fourteen out of 106 patients (13.2%) died during hospitalisation. Death was related to COVID-19 in 13 cases (93%) and related to PE in only 1 case (7%). The median interval between admission and death was 11 days (IQR 6-29). Patients who died were significantly older (median 83 years [79.5-89.5] (p=0.001)) and more of them had severe, very severe, or critical features of COVID-19 pneumonia on CTPA (p=<0.001) at admission (Table 1).

Hospital mortality in patients with confirmed PE on admission was 4/15 (26.6%) and was not statistically different compared to hospital mortality of the group without PE 10/91 (11.0%) (p=0.09) which might be primarily driven by the small study size. At 3-months, no patients were lost to follow-up and seven additional deaths occurred for a total mortality rate of 21/106 (19.8%). Of these 7 deaths, 6 were due to comorbidities and 1 was of unknown cause in an 85 year-old woman. No VTE recurrence occurred after hospital discharge in survivors.

This present study showed a prevalence of PE of 14.2%, (95%CI 7.5-20.8) at the time of hospital admission for COVID-19. In line with previous reports, our study suggests that PE is a common complication among COVID-19 patients[1,2].However, this is the first study to describe the prevalence of PE at hospital admission.

Although a high prevalence of PE is reported in ICU (20.6-27%) and at conventional wards (8.3%) in patients with COVID-19, all these studies, the reported prevalence of

PE is potentially biased since CTPA was only performed in COVID-19 patients with clinical aggravation and/or with clinical suspicion for PE and CTPA might not have been performed in intubated patients with a severe clinical course[1,7–9]. In contrast, in our study, CTPA was performed routinely on admission regardless of whether PE was clinically suspected or not.

During follow up, no other Pes were diagnosed, suggesting that looking for PE at the time of admission, and using a prophylactic anticoagulant treatment in the absence of PE, is safe and prevents new PE during the in-hospital period and 3-month follow-up period.

One of the study limitations is the relatively small number of COVID-19 admitted patients. Indeed, our study started after the lockdown setting of our region that fortunately reduced the number of COVID-19 hospitalisation. Additionally, 21.5% of patients were excluded from the study, mostly due to contraindications to iodinated contrast injection or inability to understand verbal information about the study due to dementia. Lastly, there were protocol violations because D-dimer tests were not done in 8 patients, 2 of whom had acute PE confirmed on CTPA. Large multicentre cohort studies are needed to confirm these data and explore the reasons why SARS-CoV-2 predisposes to VTE events, as no other respiratory viruses are known to do this[10–13].

In conclusion, this prospective study reported a high prevalence of PE in patients with COVID-19 at time of hospital admission. For this reason, we support CTPA exams on hospital admission in COVID-19 patients requiring supplemental oxygen, having high D-dimer concentrations or long history of COVID-19 symptoms, if no contraindicated.

1. Klok FA, Kruip 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.

2. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; 46: 1089–1098.

3. Frydman GH, Streiff MB, Connors JM, et al. The Potential Role of Coagulation Factor Xa in the Pathophysiology of COVID-19: A Role for Anticoagulants as Multimodal Therapeutic Agents. *TH Open Companion J Thromb Haemost* 2020; 4: e288–e299.

4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet Lond Engl* 2020; 395: 1054–1062.

5. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imaging* 2020; 47: 1275–1280.

6. Revel M-P, Parkar AP, Prosch H, et al. COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; 30: 4903–4909.

7. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation* 2020; 142: 184–186.

8. Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J* 2020; 41: 3058–3068.

9. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020; 191: 9–14.

10. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet Lond Engl* 2020; 395: 1417–1418.

11. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res J Lab Clin Med* 2020; 220: 1–13.

12. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120–128.

13. Bunce PE, High SM, Nadjafi M, et al. Pandemic H1N1 influenza infection and vascular thrombosis. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2011; 52: e14-17.

Table 1. Baseline characteristics and comparison between patients with PE and patients without PE.

	All patients (n=106)	Patients with PE (n=15)	Patients without PE (n=91)	P-value
Age (years) *	63 [53-82]	80.5 [53-89]	63 [52-80]	0.09
Gender, male n (%)	48 (45)	8 (53)	40 (44)	0.24
Body Mass Index (BMI) *	27 [21.5-32] (n=57)	32 [23.5-40] (n=8)	25 [21-30] (n=49)	0.39
Time from COVID symptoms to hospital admission (days)*	7 [3-15]	14 [8-22]	7 [3-15]	0.01
Patients with risk factors for VTE n (%):	32 (30)	8 (53)	26 (29)	0.10
-Malignancy / History of malignancy n (%)	16 (15)	2 (13)	14 (15)	
-Immobilization/surgery in the past 4 weeks n (%)	12 (11)	2 (13)	12 (13)	
-History of VTE n (%)	8 (7)	3 (20)	5 (5)	
-Oestrogen n (%)	2 (2)	1 (6)	1 (1)	
D-dimer concentration (ng/ml) * #	1190 [669-2245] (n=98)	3220 [2317-3855] (n=13)	1047 [620-1764] (n=96)	0.001
Oxygen needed on admission n (%)	33 (31)	9 (60)	24 (26)	0.03
CT of chest features of COVID-19 pneumonia				
- Mild (< 10 %) and moderate (10-25 %) n (%)	72 (68)	10 (67)	62 (68)	0.85
- Severe (25-50 %), very severe (50-75 %) and critical (> 75 %) n (%)	34 (32)	5 (33)	29 (32)	

* median [IQR].
# D-Dimers plasma levels were obtained using either VIDAS D-dimer Exclusion, Biomerieux or STA-LIATEST, Diagnostica Stago.
VTE= venous thromboembolism. PE= pulmonary embolism.
Data are expressed as number of occurrences, n (% of total).