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Letter to the Editors-in-Chief

## Association between Covid-19 and Pulmonary Embolism (AC-19-PE study)

Infection by SARS-Cov-2 is mainly characterized by fever and respiratory symptoms, with dyspnea and lung infiltrates in more severe cases [1]. Many patients also present with a pro-coagulant state, characterized by increased D-dimer levels and associated with increased complications and a worse prognosis [1]. Accordingly, pulmonary embolism (PE) could be more frequent in patients with COVID-19. Single center case-series reported a PE incidence of 2.6% (10/388) [2] and 8.2% (23/280) [3] in hospitalized patients and 20.6% (22/107) in patients admitted to intensive care [4]. As hospitalization itself is a risk factor for venous thromboembolism, it is not known if these PE incidences are part of the pathogenesis of SARS-Cov-2 or only occur because patients are bedridden, receiving multiple medications and in very poor condition. Focusing on patients with COVID at on arrival to the emergency department (ED), before hospitalization and the initiation of specific treatments for SARS-COV-2 infection, could help to answer this question [5,6]. In the PEPCOV study, we found that among patients at high-risk of PE undergoing a computerized tomography pulmonary arteriography (CTPA) in the ED, PE was not more frequent in COVID compared to non-COVID patients, even after adjustment for differences among patients [7]. We designed AC-19-PE (Association between COVID-19 and Pulmonary Embolism) study to further explore this hypothesis by determining whether PE is more frequently suspected by emergency physicians and whether PE is more frequently diagnosed during the COVID pandemic and in COVID-affected patients.

The AC-19-PE study was a non-interventional, retrospective review of epidemiologic and clinical data of patients attending 8 EDs (4 Spanish, 4 French; 7 of which participated in the PEPCOV study) during two time periods: one immediately before (pre-COVID period) and one immediately after (COVID period) the initiation of the COVID outbreak (March 6th in Spain, March 15th in France). For each period, we obtained the following information: 1) the number of patients attending the ED; 2) the number of patients diagnosed with COVID (clinical or microbiological diagnosis) during the COVID period, 3) the number of CTPA performed; and 4) the number of PE diagnosed. We recorded the age and sex of patients undergoing CTPA. Every CTPA was reviewed to identify PE and signs of COVID infection (if present, COVID diagnosis was also accepted). We calculated the raw odds ratio (OR) with the 95% confidence interval (95%CI) for PE suspicion (i.e., patients in whom a CTPA was ordered in the ED because of PE was suspected based on patient signs and symptoms) and diagnosis (i.e., patients in whom PE was radiologically detected in the CTPA) in the COVID versus the pre-COVID period, and in COVID versus non-COVID patients.

We analyzed 136,602 patients: 39,408 in the COVID period (153 patients/ED/day) and 97,194 in the pre-COVID period (246 patients/ED/day); 8880 were COVID patients and 127,911 non-COVID patients. The complete analysis of data regarding the number of CTPA orders and the number of patients with a finally confirmed PE, detailed by center and period, is presented in the Table 1. Although some variability was observed among individual EDs and countries, most of the risks were in the same direction as in the whole cohort. The main findings of the AC-19-PE study were the following:

1- Rate of CTPA use during COVID and pre-COVID periods: Emergency physicians ordered 1082 CTPA (1.66 CTPA/day). Mean age of patients in whom PE was suspected and CTPA was ordered was 64 years (SD: 18) and 50.8% were females. Patients attending the ED during the COVID period underwent CTPA more frequently than patients attending the ED during the pre-COVID period (13.45 vs. 5.68 CTPA/1000 ED patients, OR = 2.39, 95%CI = 2.12–2.69).
2- Rate of PE diagnosis during COVID and pre-COVID periods: A diagnosis of PE was confirmed in 177 patients (16.4% of CTPA, 0.27 PE/day). Mean age of patients with PE was 65 years (SD: 17) and 47.5% were females. Patients attending the ED during the COVID period were more frequently diagnosed with PE than patients attending the ED during the pre-COVID period (2.23 vs. 0.92 PE/1000 ED visits, OR = 2.44, 95%CI = 1.82-3.28).
3- CTPA use and PE diagnosis in COVID patients respect to non-COVID patients: The probability that a CTPA was ordered and a PE was diagnosed in the ED was higher in COVID than in non-COVID patients (OR = 6.24, 95%CI = 5.46–7.12; and OR = 7.24, 95%CI = 5.30–9.31; respectively). Specifically, PE was diagnosed in 6.64‰ of COVID patients attending the ED (95%CI = 5.06–8.56‰), and in 0.92‰ of non-COVID patients (95%CI = 0.76–1.11‰, with similar rates of PE diagnosis in non-COVID patients during the COVID and pre-COVID periods: 0.94 vs. 0.92‰, OR = 1.03, 95%CI = 0.68–1.57).
4- Overall diagnostic yield of CTPA for PE: The probability of PE diagnosis in high-risk patients in whom a CTPA was ordered in the ED did not differ between the COVID and pre-COVID periods (16.6% vs. 16.1% of PE diagnosis, OR = 1.04, 95%CI = 0.75–1.43) or between COVID and non-COVID patients (18.4% vs. 15.5%, OR = 1.23, 95%CI = 0.87–1.74).

Fig. 1 summarizes the main findings of the present study, illustrating that CTPA orders and PE diagnosis were more frequent during the COVID period and in COVID patients, although the probability of obtaining a final diagnosis in high-risk PE patients (i.e., those in whom a CTPA was ordered) was the same in both periods and in both groups of patients.

The frequency of PE in COVID patients attending the ED is 6.64‰ (95%CI = 5.06–8.56‰), which was more than 7-fold higher than that in the non-COVID ED population. This relatively high rate suggests that during the COVID period, the ED population comprised more patients with suspected and diagnosed PE, due, in part, to a higher suspicion by emergency physicians and also to fewer ED visits for other complaints (due to lockdown measures). However, some study limitations impose caution in interpreting our findings. In many cases the diagnosis of COVID was based on clinical/radiological findings, with no

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**Table 1**
Raw data and derived ratios of the eight emergency departments participating in the AC-19-PE study, globally and by country (Spain and France) and by individual center.

| | SPAINISH EMERGENCY DEPARTMENTS | | | | | FRENCH EMERGENCY DEPARTMENTS | | | | | Grand TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | H1 (Alicante) | H2 (Mar) | H3 (Clínic) | H4 (Sant Pau) | TOTAL (Spanish) | H1 (A Paré) | H2 (Strasbourg) | H3 (Rouen) | H4 (Nancy) | TOTAL (French) | |
| **ROW DATA** | | | | | | | | | | | |
| **Days reviewed** | **107** | **93** | **85** | **86** | **371** | **71** | **70** | **70** | **71** | **282** | **653** |
| COVID / Pre-COVID period* | 42 / 65 | 36 / 57 | 34 / 51 | 36 / 50 | 148 / 223 | 28 / 43 | 27 / 43 | 27 / 43 | 28 / 43 | 110 / 172 | 258 / 395 |
| **Patients attending ED** | **22,711** | **27,536** | **22,460** | **23,824** | **96,531** | **6,124** | **12,433** | **14,419** | **7,095** | **40,071** | **136,602** |
| COVID / Pre-COVID period* | 5,737 / 16,974 | 8,737 / 18,799 | 6,637 / 15,823 | 6,890 / 16,934 | 28,001 / 68,530 | 1,652 / 4,472 | 3,618 / 8,815 | 4,065 / 10,354 | 2,072 / 5,023 | 11,407 / 28,664 | 39,408 / 97,194 |
| COVID / non-COVID patients | 1,370 / 21,341 | 1,579 / 25,966 | 1,942 / 20,518 | 2,304 / 21,520 | 7,195 / 89,345 | 190 / 5,934 | 957 / 11,476 | 306 / 14,113 | 232 / 7,043 | 1,685 / 38,566 | 8,880 / 127,911 |
| **Suspected PE**(CTPA performed) | **113** | **88** | **116** | **82** | **399** | **90** | **158** | **338** | **97** | **683** | **1,082** |
| COVID / Pre-COVID period* | 41 / 72 | 46 / 42 | 44 / 72 | 47 / 35 | 178 / 221 | 31 / 59 | 65 / 93 | 167 / 171 | 89 / 8 | 352 / 331 | 530 / 552 |
| COVID / non-COVID patients | 31 / 82 | 26 / 62 | 34 / 82 | 37 / 45 | 128 / 271 | 20 / 70 | 60 / 98 | 64 / 274 | 48 / 49 | 192 / 491 | 320 / 762 |
| **Confirmed PE** | **15** | **25** | **31** | **17** | **88** | **9** | **23** | **53** | **4** | **89** | **177** |
| COVID / Pre-COVID period* | 5 /10 | 15 / 10 | 18 / 13 | 11 / 6 | 49 / 39 | 3 / 6 | 14 / 9 | 19 / 34 | 3 / 1 | 39 / 50 | 88 / 89 |
| COVID / non-COVID patients | 1 / 14 | 9 / 16 | 12 / 19 | 7 / 10 | 29 / 59 | 3 / 6 | 9 / 14 | 9 / 44 | 4 / 0 | 30 / 59 | 59 / 118 |
| **Patients attending ED per day** | **212** | **296** | **264** | **277** | **260** | **86** | **178** | **206** | **100** | **142** | **209** |
| COVID / Pre-COVID period* | 137 / 261 | 243 / 330 | 195 / 310 | 191 / 339 | 189 / 307 | 59 / 104 | 134 / 205 | 151 / 241 | 74 / 117 | 104 / 167 | 153 / 246 |
| **Suspected PE per day** | **1.06** | **0.95** | **1.36** | **0.95** | **1.08** | **1.27** | **2.26** | **4.83** | **1.37** | **2.42** | **1.66** |
| COVID / Pre-COVID period* | 0.98 / 1.11 | 1.28 / 0.74 | 1.29 / 1.41 | 1.31 / 0.70 | 1.20 / 0.99 | 1.11 / 1.37 | 2.41 / 2.16 | 6.19 / 3.98 | 3.18 / 0.19 | 3.20 / 1.92 | 2.05 / 1.40 |
| **Confirmed PE per day** | **0.14** | **0.27** | **0.36** | **0.20** | **0.24** | **0.13** | **0.33** | **0.76** | **0.06** | **0.32** | **0.27** |
| COVID / Pre-COVID period* | 0.11 / 0.15 | 0.42 / 0.18 | 0.53 / 0.25 | 0.31 / 0.12 | 0.33 / 0.17 | 0.11 / 0.14 | 0.52 / 0.21 | 0.70 / 0.79 | 0.11 / 0.02 | 0.35 / 0.29 | 0.34 / 0.23 |
| **RATIOS** | | | | | | | | | | | |
| **Suspected PE per 1000 ED patients** | **4.98** | **3.20** | **5.16** | **3.44** | **4.13** | **14.70** | **12.71** | **24.44** | **13.67** | **17,04** | **7.92** |
| COVID / Pre-COVID period* | 7.15 / 4.24 | 5.26 / 2.23 | 6.63 / 4.55 | 6.82 / 2.07 | 6.36 / 3.22 | 18.8 / 13.2 | 18.0 / 10.6 | 41.1 / 16.5 | 43.0 / 1.6 | 30.9 / 11.5 | 13.45 / 5.68 |
| *OR (95% CI) for COVID period* | *1.69 (1.15-2.48)* | *2.36 (1.55-3.59)* | *1.46 (1.00-2.13)* | *3.32 (2.14-5.14)* | *1.98 (1.62-2.41)* | *1.43 (0.92-2.22)* | *1.72 (1.25-2.36)* | *2.55 (2.06-3.17)* | *28.1 (13.6-58.2)* | *2.72 (2.34-3.17)* | ***2.39 (2.12-2.69)*** |
| COVID / non-COVID patients | 22.63 / 3.84 | 16.47 / 2.39 | 17.51 / 4.00 | 16.06 / 2.09 | 17.79 / 3.03 | 105.3 / 11.80 | 62.70 / 8.54 | 209.2 / 19.41 | 206.9 / 6.96 | 113.9 / 12.73 | 36.04 /5.96 |
| *OR (95% CI) for COVID patients* | *5.96 (3.93-9.04)* | *7.00 (4.41-11.1)* | *4.44 (2.97-6.64)* | *7.79 (5.03-12.1)* | *5.95 (4.82-7.36)* | *9.85 (5.86-16.6)* | *7.77 (5.59-10.8)* | *13.4 (9.89-18.0)* | *37.2 (24.4-56.9)* | *9.97 (8.37-11.9)* | ***6.24 (5.46-7.12)*** |
| **Confirmed PE per 1000 ED patients** | **0.66** | **0.91** | **1.38** | **0.71** | **0.91** | **1.47** | **1.85** | **3.68** | **0.56** | **2.22** | **1.30** |
| COVID / Pre-COVID period* | 0.87 / 0.59 | 1.72 / 0.53 | 2.71 / 0.82 | 1.60 / 0.35 | 1.75 / 0.57 | 1.82 / 1.34 | 3.87 / 1.02 | 4.67 / 3.28 | 1.45 / 0.20 | 3.42 / 1.74 | 2.23 / 0.92 |
| *OR (95% CI) for COVID period* | *1.48 (0.50-4.33)* | *3.20 (2.45-7.20)* | *3.31 (1.62-6.76)* | *4.51 (1.66-12.21)* | *3.08 (2.02-4.69)* | *1.35 (0.34-5.42)* | *3.08 (1.64-8.79)* | *1.43 (0.81-2.50)* | *7.28 (0.76-70.1)* | *1.93 (1.29-2.99)* | ***2.44 (1.82-3.28)*** |
| COVID / non-COVID patients | 0.73 / 0.66 | 5.70 / 0.62 | 6.18 / 0.93 | 3.04 / 0.46 | 4.03 / 0.66 | 15.79 / 1.01 | 9.40 / 1.22 | 29.41 / 3.12 | 17.24 / 0 | 17.80 / 1.53 | 6.64 / 0.92 |
| *OR (95% CI) for COVID patients* | *1.11 (0.15-8.47)* | *9.30 (4.10-21.1)* | *6.71 (3.25-13.8)* | *6.56 (2.49-17.2)* | *6.12 (3.92-9.56)* | *15.9 (3.93-63.9)* | *7.77 (3.36-18.0)* | *9.69 (4.69-20.0)* | *Not calculable* | *11.8 (7.60-18.4)* | ***7.24 (5.30-9.91)*** |
| **Confirmed PE per 100 suspected PE** | **13.3** | **28.4** | **26.7** | **20.7** | **22.1** | **10.0** | **14.6** | **15.7** | **4.1** | **13.0** | **16.4** |
| COVID / Pre-COVID period* | 12.2 / 13.9 | 32.6 / 23.8 | 40.9 / 18.1 | 23.4 / 17.1 | 27.5 / 17.6 | 9.7 / 10.2 | 21.5 / 9.7 | 11.4 / 19.9 | 3.4 / 12.5 | 11.1 / 15.1 | 16.6 / 16.1 |
| *OR (95% CI) for COVID period* | *0.86 (0.27-2.72)* | *1.55 (0.60-3.97)* | *3.14 (1.34-7.35)* | *1.48 (0.49-4.48)* | *1.77 (1.10-2.86)* | *0.94 (0.22-4.08)* | *2.56 (1.03-6.35)* | *0.51 (0.28-0.95)* | *0.24 (0.02-2.67)* | *0.70 (0.45-1.10)* | ***1.04 (0.75-1.43)*** |
| COVID / non-COVID patients | 3.2 / 17.1 | 34.6 / 25.8 | 35.3 / 23.2 | 18.9 / 22.2 | 22.6 / 21.8 | 15.0 / 8.6 | 11.3 / 14.3 | 14.1 / 16.1 | 8.3 / 0 | 15.6 / 12.0 | 18.4 / 15.5 |
| *OR (95% CI) for COVID patients* | *0.16 (0.02-1.29)* | *1.52 (0.57-4.09)* | *1.05 (0.45-2.44)* | *0.82 (0.28-2.41)* | *1.05 (0.64-1.74)* | *1.88 (0.43-8.32)* | *1.06 (0.43-2.62)* | *0.86 (0.39-1.86)* | *Not calculable* | *1.36 (0.84-2.18)* | ***1.23 (0.87-1.74)*** |

*The starting day for patient inclusion varied among centers between January 15th and February 1st, 2020. The finishing day for patient inclusion in the COVID period varied among centers between April 10th and April 15th, 2020. The day starting the COVID period was fixed as the day when patient 100 was diagnosed in each country (6th March in Spain, 15th March in France). OR and 95% CI reported in red numbers denote statistical significance. OR: odds ratio; CI: confidence interval; PE: pulmonary embolism; ED: emergency department.

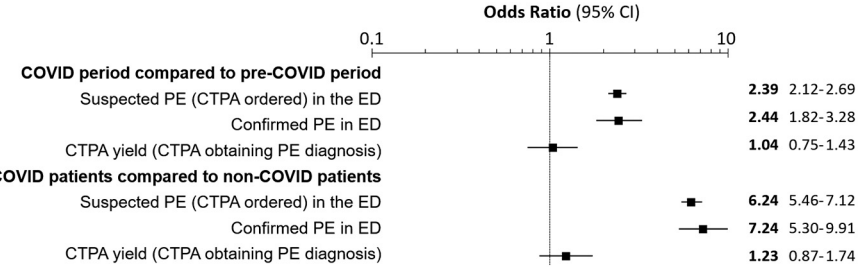


**Fig. 1.** Summary of the main findings of the AC-19-PE study.
CTPA: computerized tomography pulmonary angiogram; ED: emergency department; PE: pulmonary embolism.

microbiological confirmation. Further PE was only counted for study purposes if a CTPA was performed in the ED. During the COVID-19 pandemic, emergency physicians had a lower threshold for ordering CTPA (OR = 2.39), although CTPA positivity for PE did not differ between periods (OR = 1.04), confirming that SARS-COV-2 is not associated with a higher incidence of PE among high risk patients [7]. However, a higher proportion of ED patients were diagnosed with PE during the COVID period (OR = 6.24) and among COVID patients (OR = 7.24) when all ED comers (and not just high-risk patients) were taken into account. Patient-related or disease-related factors could have accounted for such increased rates, as the characteristics of the patients attending the ED could be dissimilar between periods, although the similar rates observed for non-COVID patients in both periods (OR = 1.03) does not support this possibility.

## Contribution of authors

OM and YF discussed the idea and design of study. All authors provided patients to the study. Data analysis and first draft writing was done be OM. All authors read this draft and provided insight for the final version. OM is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to publication.

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## Declaration of competing interest

None author reported any conflict of interest directly or indirectly connected with this manuscript.

## References

[1] 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.C. Hui, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720.

[2] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, N. Kucher, J.D. Studt, C. Sacco, B. Alexia, et al., Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thromb. Res. 191 (2020) 9–14.

[3] F. Grillet, J. Behr, P. Calame, S. Aubry, E. Delabrousse, Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography, Radiology (2020), https://doi.org/10.1148/radiol.2020201544 (in press).

[4] J. Poissy, J. Goutay, M. Caplan, E. Parmentier, T. Duburcq, F. Lassalle, E. Jeanpierre, A. Rauch, J. Labreuche, S. Susen, et al., Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence, Circulation (2020), https://doi.org/10.1161/CIRCULATIONAHA.120.047430 (in press).

[5] O. Miró, J. González Del Castillo, Collaboration among Spanish emergency departments to promote research: on the creation of the SIESTA (Spanish Investigators in Emergency Situations TeAm) network and the coordination of the UMC-19 (Unusual Manifestations of COVID-19) macroproject, Emergencias. 32 (2020) 269–277.

[6] S. Jiménez Hernández, L. Lozano Polo, G. Suñen Cuquerella, B. Peña Pardo, B. Espinosa, C. Cardozo, et al., Clinical findings, risk factors, and final outcome in patients diagnosed with pulmonary thromboembolism and COVID-19 in hospital emergency departments, Emergencias 32 (2020) 253–257.

[7] Y. Freund, M. Drogrey, O. Miró, A. Marra, A.L. Féral-Pierssens, A. Penaloza, B.A. Lara Hernandez, S. Beaune, J. Gorlicki, P. VattinadaAyar, et al., Association between Pulmonary Embolism and COVID-19 in ED 1 patients: the PEPCOV international retrospective study, Acad. Emerg. Med. 27 (2020) 811–820.

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