



**HAL**  
open science

# Association Between Pulmonary Embolism and COVID-19 in Emergency Department Patients Undergoing Computed Tomography Pulmonary Angiogram: The PEPCOV International Retrospective Study

Yonathan Freund, Marie Drogrey, Òscar Miró, Alessio Marra, Anne-Laure Féral-Pierssens, Andrea Penaloza, Barbara Hernandez, Sebastien Beaune, Judith Gorlicki, Prabakar Vaittinada Ayar, et al.

## ► To cite this version:

Yonathan Freund, Marie Drogrey, Òscar Miró, Alessio Marra, Anne-Laure Féral-Pierssens, et al.. Association Between Pulmonary Embolism and COVID-19 in Emergency Department Patients Undergoing Computed Tomography Pulmonary Angiogram: The PEPCOV International Retrospective Study. *Academic Emergency Medicine*, 2020, 27 (9), pp.811-820. 10.1111/acem.14096 . hal-02948943

**HAL Id: hal-02948943**

**<https://hal.sorbonne-universite.fr/hal-02948943>**

Submitted on 25 Sep 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1       **Association between Pulmonary Embolism and COVID-19 in ED**  
2       **patients undergoing CTPA: the PEPCOV international retrospective**  
3       **study**

4  
5       Yonathan Freund, MD; PhD (1,2), Marie Drogrey, MD (2), Òscar Miró, MD, PhD (3),  
6       Alessio Marra MD (4), Anne-Laure Féral-Pierssens, MD, PhD (5), Andrea Penalzoa,  
7       PD, PhD (6), Barbara A Lara Hernandez, MD (7), Sebastien Beaune, MD, PhD (8),  
8       Judith Gorlicki, MD (9), Prabakar Vattinada Ayar, MD (10), Jennifer Truchot, MD,  
9       PhD (11), Barbara Pena, MD (12), Alfons Aguirre, MD, PhD (13), Florent Fémy, MD  
10       (14), Nicolas Javaud, MD, PhD (15), Anthony Chauvin, Md, PhD (16), Tahar  
11       Chouihed, MD, PhD (17), Emmanuel Montassier, PD, PhD (18), Pierre-Géraud  
12       Claret, MD, PhD (19), Céline Occelli, MD (20), Mélanie Roussel, MD (21), Fabien  
13       Brigant, MD (22), Sami Ellouze, MD, PhD (23), Pierrick Le Borgne, MD (24), Said  
14       Laribi, MD, PhD (25), Tabassome Simon, MD, PhD (1, 26), Olivier Lucidarme, MD,  
15       PhD (1, 27), Marine Cachanado, MsC (26), Ben Bloom, MD, PhD (28), and the  
16       IMPROVING EMERGENCY CARE FHU Collaborators.

17       1. Sorbonne Université, Paris, France

18       2. Emergency department, Hôpital Pitié-Salpêtrière, Assistance Publique - Hôpitaux  
19       de Paris (APHP), APHP.SU, Paris, France

20       3. Emergency Departement, Hospital Clínic, Barcelona, Catalonia, Spain

21       4. Emergency Department, Centro EAS - Emergenza Alta Specializzazione, ASST  
22       Papa Giovanni XXIII Hospital, Bergamo, Italy

23       5. Charles Lemoyne - Saguenay Lac Saint-Jean research center on health  
24       innovations (CR CSIS), Sherbrooke University, Longueuil, Québec, Canada;  
25       Emergency Department, european Georges Pompidou hospital, APHP, Paris, France

26       6. Service des Urgences, Cliniques Universitaires Saint-Luc, Université catholique  
27       de Louvain

28       7. Emergency Medicine Section. Pontificia Universidad Católica de Chile, Santiago,  
29       Chile

30       8. Emergency department, Hôpital Ambroise-Paré, APHP, Boulogne, inserm UMR  
31       1144, université Paris Centre, France

32       9. Emergency Department, SAMU 93, Avicenne University Hospital,  
33       APHP.HUPSSD, Bobigny, France. Inserm UMR-S 942, Sorbonne Paris Nord  
34       University, Bobigny, France.

35       10. Emergency Department, University Hospital of Beaujon, APHP, Clichy,  
36       France;UMR-S 942, INSERM, MASCOT, Paris ; University, Paris, France.

- 37 11. Emergency Department, Cochin Hospital, Hôpitaux Universitaire Paris Centre,  
38 APHP, Paris, France.
- 39 12. Emergency Department, Hospital General Universitario de Alicante, Alicante,  
40 Spain.
- 41 13. Emergency Department, Hospital del Mar, Barcelona, Catalonia, Spain
- 42 14. Emergency department, Georges Pompidou European Hospital, APHP,  
43 Université de Paris, Paris, France. Toxicology and Chemical Risks Department,  
44 French Armed Forces Biomedical Institute, Bretigny-Sur-Orges, France
- 45 15. Emergency Department, Louis Mourier Hospital, University of Paris,  
46 APHP.North, Paris, France
- 47 16. Emergency Department, Hopital Lariboisière, Assistance Publique-Hôpitaux de  
48 Paris, Paris, France; Faculté de Médecine, Université de Paris, France
- 49 17. Université de Lorraine, Emergency Department, University Hospital of Nancy,  
50 Centre d'Investigations Cliniques- 1433, and Inserm UMR\_S 1116; F-CRIN INI-  
51 CRCT, Nancy, France.
- 52 18. Department of Emergency Medicine, CHU Nantes, 44000-Nantes, France,  
53 MiHAR Laboratory, Université de Nantes, 44000-Nantes, France
- 54 19. Department of Anesthesia Resuscitation Pain Emergency Medicine, Nîmes  
55 University Hospital
- 56 20. Emergency Department, CHU Pasteur 2, Nice, France ; University Nice Côte  
57 d'Azur, France.
- 58 21. Emergency Department, Rouen University Hospital, F-76000 Rouen, France.
- 59 22. Emergency department, Hôpital Saint-Antoine, APHP.SU, Paris, France
- 60 23. Emergency department, Hôpital Saint-Louis, APHP, Paris, France
- 61 24. Emergency Department, Hôpitaux Universitaires de Strasbourg, F-67000  
62 Strasbourg, France and INSERM (French National Institute of Health and Medical  
63 Research), UMR 1260, Regenerative NanoMedicine (RNM), Fédération de Médecine  
64 Translational (FMTS), University of Strasbourg, Strasbourg, France
- 65 25. Emergency Medicine Department, School of Medicine and CHU Tours, Tours  
66 University, France
- 67 26. Clinical research platform(URC-CRC-CRB), AP-HP Hôpital Saint-Antoine, ,  
68 Paris, France
- 69 27. APHP-Sorbonne Universités, Pitié salpêtrière hospital, Radiology department and  
70 UPMC Univ Paris 06, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, F-  
71 75013, Paris, France
- 72 28. Emergency Department, Royal London Hospital, Barts Health NHS Trust,  
73 London, UK
- 74 Corresponding author: Pr Yonathan Freund, Service d'accueil des urgences, 47-83  
75 Bd de l'hôpital, 75013 Paris, France. Tel: +33 1 84 82 71 29 Fax: + 33 1 42 17 70 10  
76 Email: [yonathan.freund@aphp.fr](mailto:yonathan.freund@aphp.fr)

77

78 The authors declare they have no conflict of interest with this study.

79 There were no funding for this study.

80 Word count: 2341                      Figure count: 1                      Table count: 4

81

82

83 **IMPROVING EMERGENCY CARE FHU Collaborators group**

84 H el ene Goulet MD, H opital Tenon, APHP, Paris

85 Benoit Ghaye , MD,PhD, Service de Radiologie, Cliniques Universitaires Saint-Luc,  
86 Universit  catholique de Louvain

87 Leslie Sgorlon, MD (Department of Anesthesia Resuscitation Pain Emergency  
88 Medicine, N imes University Hospital)

89 Julien Frandon, MD (Department of Radiology, Medical Imaging Group N imes,  
90 N imes University Hospital)

91 Matthieu Demeyere, MD Department of Radiology, Rouen University Hospital, F-  
92 76000 Rouen, France

93 Xavier Eyer (Emergency Departement, Hopital Lariboisi re, Assistance Publique-  
94 H opitaux de Paris, Paris, France; Facult  de M decine, Universit  de Paris, France)

95 Adrien Bassand, MD: Emergency Department, University Hospital of Nancy, Nancy,  
96 France.

97 Romain Gillet, MD, Guilloz imaging department, Central Hospital, University Hospital  
98 of Nancy, Nancy, France

99 Pablo Aguilera, MD, Emergency Section Chair, Red de Salud UC Christus Health,  
100 Pontificia Universidad Cat lica de Chile, Santiago, Chile.

101 Pedro Antonio Gondim Teixeira, MD, PhD, Guilloz imaging department, Central  
102 Hospital, University Hospital of Nancy, Nancy, France

103 Anne Laure Gaultier, MD, Departments of Radiology, Georges Pompidou European  
104 Hospital, Assistance Publique - H opitaux de Paris.

105 Jean-Marc Chauny, MD, Emergency Department, Research Centre, H opital du  
106 Sacr -Coeur de Montr al (CIUSSS du Nord de-l' le-de-Montr al), Montr al, Qu bec,  
107 Canada.

108 Pascal Bilbault, MD, PhD, Emergency Department, H opitaux Universitaires de  
109 Strasbourg, and INSERM UMR 1260, Regenerative NanoMedicine (RNM),  
110 F d ration de M decine Translationnelle (FMTS), University of Strasbourg,  
111 Strasbourg, France

- 112 Carlos Cardozo, MD, Emergency Department, Hospital Clínic, Barcelona, Catalonia,  
113 Spain
- 114 Pere Llorens, MD. PhD, Emergency Department, Hospital General Universitario de  
115 Alicante, Alicante, Spain
- 116 Lorenzo Della Bella, MD; Federico Zanardi, MD; Carlo Preti, MD; Cosentini Roberto,  
117 MD; Andrea Della Bella, MD; Carlo Pretti, MD, from Emergency Department, Centro  
118 EAS - Emergenza Alta Specializzazione, ASST Papa Giovanni XXIII Hospital,  
119 Bergamo, Italy
- 120 Samia Boussouar, MD, APHP-Sorbonne Universités, Pitié Salpêtrière Hospital,  
121 radiology department, F-75013, Paris, France
- 122 Victoria Donciu, MD, APHP-Sorbonne Universités, Pitié Salpêtrière Hospital,  
123 radiology department, F-75013, Paris, France
- 124 Alban Redheuil, MD, PhD, APHP-Sorbonne Universités, Pitié salpêtrière hospital,  
125 Radiology department and UPMC Univ Paris 06, CNRS, INSERM, Laboratoire  
126 d'Imagerie Biomédicale, F-75013, Paris, France
- 127 Léa Legay, MD, Emergency Department, Hôpital Saint-Louis, Assistance Publique -  
128 Hôpitaux de Paris, APHP, Paris, France
- 129 Olivier Peyrony, MD, PhD, Hôpital Saint-Louis, Assistance Publique - Hôpitaux de  
130 Paris, APHP, Paris, France
- 131 Ernesto Escobedo Carvajal
- 132 Emergency Medicine Section. Pontificia Universidad Católica de Chile, Santiago,  
133 Chile
- 134 Arthur DAVID, Central Department of Radiology and Medical Imaging, CHU Nantes,  
135 44000-Nantes, France
- 136 Bousson Valérie Service d'Imagerie Ostéo-Articulaire, Viscérale et Vasculaire,  
137 Hôpital Lariboisière, APHP.Nord, Paris and Laboratoire de Biologie, Bioingénierie et  
138 Bioimagerie Ostéo-Articulaires (B3OA), UMR CNRS 7052, INSERM U1271.  
139 Université de Paris
- 140 Laurent Brunereau, MD PHD, Service Imagerie, CHU de Tours.
- 141 Sophie Dabin-Pouchard, IRC, Département de médecine d'Urgence, CHU de Tours
- 142 Isabel Cirera, MD PhD, Emergency Department, hospital del mar, Barcelona, Spain.  
143

144 **Abstract (Word count 276)**  
145

146 **Background:** There have been reports of pro-coagulant activity in patients with  
147 COVID-19. Whether there is an association between pulmonary embolism (PE) and  
148 COVID-19 in the emergency department (ED) is unknown. The aim of this study was  
149 to assess whether COVID-19 is associated with PE in ED patients that underwent a  
150 CTPA?

151 **Methods:** A retrospective study in 26 EDs from 6 countries. ED patients in whom a  
152 computed tomographic pulmonary angiogram (CTPA) was performed for suspected  
153 PE during a 2-month period covering the pandemic peak. The primary endpoint was  
154 the occurrence of a pulmonary embolism on CTPA. COVID-19 was diagnosed in the  
155 ED either on CT or RT-PCR. A multivariable binary logistic regression was built to  
156 adjust with other variables known to be associated with PE. A sensitivity analysis was  
157 performed in patients included during the pandemic period.

158 **Results:** A total of 3358 patients were included, of whom 105 were excluded  
159 because COVID-19 status was unknown, leaving 3253 for analysis. Among them,  
160 974 (30%) were diagnosed with COVID-19. Mean age was 61 years (19) and 52%  
161 were women. A pulmonary embolism was diagnosed on CTPA in 500 patients (15%).  
162 The risk of PE was similar between COVID-19 patients and others (15% in both  
163 groups). In the multivariable binary logistic regression model, COVID-19 was not  
164 associated with higher risk of PE (adjusted odds ratio 0.98, 95% confidence interval  
165 0.76 to 1.26). There was no association when limited to patients in the pandemic  
166 period.

167 **Conclusion:** In ED patients that underwent CTPA for suspected PE, COVID-19 is  
168 not associated with an increased probability of PE diagnosis. These results were also

169 valid when limited to the pandemic period. However, these results may not apply to  
170 patients with suspected COVID-19 in general.

171 **Introduction**

172

173 COVID-19 is currently one of the greatest worldwide threats to public health, and a  
174 challenge for researchers and physicians. The reported mortality ranges from 0.1% to  
175 8% depending on the disease severity.<sup>1</sup> COVID-19 viral pneumonia is associated  
176 with hypoxia, a hyper-inflammatory state and coagulopathy.<sup>2,3</sup> High rates of elevated  
177 D-dimers have also been reported in case series, which may be associated with  
178 worse outcomes.<sup>4,5</sup> Rapid identification of patients with COVID-19 who are at risk of  
179 pulmonary embolism (PE) may improve prognosis by early initiation of anticoagulant  
180 therapy.<sup>6</sup>

181 In the emergency department (ED), the diagnostic strategy for PE is well established.  
182 Several clinical decision rules (CDR) have been validated to safely limit the use of  
183 irradiative imaging studies (especially computed tomography pulmonary angiogram  
184 [CTPA], considered as the gold standard). These CDR are based on a Bayesian  
185 approach that combines pre-test probability (i.e. suspected PE prevalence in the  
186 studied population estimated by a score or physician gestalt) with the D-dimer result  
187 to stratify risk and guide indication for CTPA. Application of the Pulmonary Embolism  
188 Rule Out Criteria (PERC) may safely exclude PE in patients with low clinical  
189 probability.<sup>7</sup> Other CDR such as the Wells or revised Geneva scores (RGS) are also  
190 recommended, and the recent YEARS protocol may allow the D-dimer threshold to  
191 be raised whilst still safely limiting the use of CTPA.<sup>8-10</sup> All these rules were validated  
192 before the COVID-19 pandemic, and their safety is based on estimated PE  
193 prevalence in the studied population. Since COVID-19 is reportedly associated with  
194 an increased risk of thrombo-embolic events, and the validity of these CDR is  
195 unknown, it is possible that during this pandemic, conventional ED diagnostic  
196 strategies for PE is unsafe. Furthermore, since decision rules are derived in specified



197 populations, a rule that applies to a stratified subpopulation of ED patients may also  
198 not extrapolate to the general population. Conversely, even if COVID-19 causes an  
199 increase in the risk of venous thromboembolism in the general population, this may  
200 not translate into a higher risk among ED patients with suspicion of PE. The aim of  
201 our study is to assess if COVID-19 is associated with PE in ED patients who  
202 underwent a CTPA for suspected PE, and to assess whether RGS based diagnostic  
203 strategy is safe in this period.

204

## 205 **Methods**

206

### 207 **Design**

208 This was a multicenter retrospective study in 26 centers from France, Spain,  
209 Belgium, Italy, Chile and Canada. The study was approved by the steering committee  
210 of Assistance Publique – Hôpitaux de Paris. Local ethics committees in all  
211 participating countries approved the study. Due to its retrospective nature on de-  
212 identified data, an informed consent was waived in all participating countries.

### 213 **Patients and data**

214 All patients who underwent a CTPA for suspected PE during the study period were  
215 included. Roughly, the COVID-19 peaks of ED visits ranged from late March to mid-  
216 April 2020. Since we wished to include patients from both prior to and during the  
217 COVID-19 pandemic, the overall study period was comprised between February 1<sup>st</sup>  
218 to April 10<sup>th</sup> 2020. The study period slightly differed in the different centers as the  
219 COVID-19 pandemic peak occurred at different periods in the participating centers. In  
220 each country, we considered that COVID-19 epidemic started when more than 100

221 patients were diagnosed positive, respectively March 4<sup>th</sup>, 6<sup>th</sup>, 15<sup>th</sup>, 15<sup>th</sup>, 18<sup>th</sup> and 24<sup>th</sup>  
222 in Italy, Spain, France, Chile, Belgium and Quebec.

223 All CTPA performed for ED patients during this period were collected, and data from  
224 the ED visits were collected. Patients with no COVID-19 status, inconclusive CTPA  
225 for the diagnosis of PE, or in whom CTPA was performed for a reason other than  
226 “suspicion of PE” were excluded.

227 Study data were obtained from the electronic health system of each center by local  
228 study investigators. Baseline characteristics, risk factors for PE and items from  
229 conventional CDR were collected.

### 230 **Objectives and endpoint**

231 The primary objective of this study was to assess whether COVID-19 was  
232 independently associated with PE in ED patients that underwent a CTPA. Secondary  
233 objectives included the validation of conventional diagnostic strategies using a  
234 combination of the Revised Geneva Score (RGS) and D-dimer in this period (Table  
235 1), and to assess the diagnostic performance of D-Dimer amongst COVID-19  
236 patients.

237 The primary endpoint was the presence of a pulmonary embolism on CTPA. Each  
238 CTPA was analyzed and interpreted by senior Radiologist.

239 In cases of inconclusive CTPAs, the patient was excluded from analysis. COVID-19  
240 status was defined with the following rule:

- 241 - Negative during the pre-pandemic period (defined as first 100 diagnosed  
242 cases in the country)
- 243 - Positive if RT-PCR was positive

244 - Positive if lung CT showed evidence of a COVID-19 lesion, i.e. ground-glass  
245 opacities or crazy paving.<sup>11</sup>

246 In cases where RT-PCR was not performed and CT was indeterminate or with non-  
247 specific abnormalities, the patient was excluded because his/her COVID-19 status  
248 could not be determined. In the absence of positive RT-PCR, a patient with CT  
249 interpreted as “unlikely COVID-19” was considered as non Covid-19. In these  
250 patients, severity of CT lesions were not reported. Severity of COVID-19 lesions were  
251 graded as recommended by French Society of Radiology and other reports as  
252 moderate (extent <25), extended (25%-<50%), severe (50%-75%) and critical (>  
253 75%).<sup>12,13</sup>

254 A simplified RGS was calculated using data collected during the ED visit (Table 1).  
255 Due to the retrospective nature of collected data, we merged the two items “unilateral  
256 lower-limb pain” and “pain on lower-limb deep venous palpation and unilateral  
257 edema” as “clinical signs of deep venous thrombosis”, with a weighting of 2 points. D-  
258 dimer, C-reactive protein and leucocytes were also collected. CT findings were  
259 classified according to their probability of COVID-19 (likely, compatible, unlikely) and  
260 their severity (mild, moderate, severe, critical).<sup>14</sup>

## 261 **Statistical Analysis**

262 Baseline characteristics were expressed as number (%) for categorical variables and  
263 mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous  
264 variables, depending on their distribution. Separate bivariate analyses were  
265 performed to determine the unadjusted association between PE and the following  
266 known risk factors: age, sex, heart rate, previous thrombo-embolic event,  
267 hemoptysis, clinical signs of deep venous thrombosis, estrogen intake and

268 surgery/immobilization within four weeks. In addition, severity of COVID-19 symptom,  
269 period (before/after pandemic onset) and country of admission were studied too. A  
270 direct multivariable binary logistic regression model was built taking into account all  
271 known risk factors: : age, sex, heart rate, previous thrombo-embolic event,  
272 hemoptysis, clinical signs of deep venous thrombosis, estrogen intake and  
273 surgery/immobilization within four weeks (P value inferior or equal to 0.2 in univariate  
274 analysis or forced into the model), and in addition center of admission.  
275 Multicollinearity was investigated using in first correlation matrix and in second  
276 tolerance and variation inflation parameters. Due to  
277 violation of linearity in the logic for age as a continuous variable, it was categorized in  
278 the model using quartile values.. Receiver-operating characteristic (ROC) curve and  
279 Youden index were used to calculate the optimal cut-off of D-dimers for PE  
280 diagnosis. Several goodness-of-fit tests were performed to determine model  
281 performance (Hosmer-Lemeshow test, Standard Pearson test, Osius-test,  
282 McCullagh-test, Informative Matrix (IM) test and Unweighted Sum of Squares test).

283 To validate the safety of a RGS-based diagnostic strategy, we compared the rate of  
284 PE diagnosed in patients with low to intermediate RGS RGS and D-dimer below the  
285 age-adjusted threshold (i.e. 500 µg/ml under 50 years, and age x 10 over 50 years)  
286 in patients with and without COVID-19.<sup>15,16</sup>

287 Since physicians' threshold for ordering a CTPA may have changed during the  
288 pandemic period, we ran a sensitivity analysis limited to patients in this period.

289 P values <0.05 were considered significant. SAS V.9.4 software (SAS Institute Inc.,  
290 Cary, NC) was used for statistical analyses.

291

292

293 **Results**

294 During the study period, 3,358 patients were included in the 26 participating EDs,  
295 52% of whom were included during the pandemic period. Amongst them, COVID-19  
296 status could not be determined in 105 patients (figure 1). A total of 3,253 were  
297 analyzed. The mean age was 61 years (SD 19) and 1,695 (52%) were women.  
298 Baseline characteristics are reported in table 2. There was no difference in patient  
299 characteristic between the two periods pre/post pandemic (Suppl table 1). Nine  
300 hundred and seventy four patients were diagnosed with COVID-19; 530 (54%) were  
301 diagnosed with both positive RT-PCR and CT, 370 (38%) on CT only and 74 (8%)  
302 only with RT-PCT.

303 Pulmonary embolism was diagnosed in 500 patients (15%); 148 patients (15%) had a  
304 COVID-19 diagnosis and 352 (15%) did not (difference 0.3% [95% confidence  
305 interval [CI] -3% to 3%], unadjusted odds ratio 0.98 [95% CI 0.78 – 1.19]). Amongst  
306 the 500 patients with PE, 59 (15%) were isolated sub-segmental,. A RGS of 5 or  
307 more (considered as high risk) was associated with a higher risk of PE (23% vs 14%,  
308 difference 9% [95%CI 1.5% to 15.7%]).

309 In the multivariable logistic regression analysis, there was no association between  
310 COVID-19 and PE (adjusted OR = 0.98, 95% CI 0.761 to 1.26). Hosmer-Lemeshow  
311 p-value was 0.40. The other goodness-of-fit tests had a  $p > 0.05$  except for IM test  
312 ( $p = 0.01$ ) There was no period effect between pre and post pandemic onset date (OR  
313 1.02, 95%CI 0.83 to 1.24,  $p = 0.72$ ). The sensitivity analysis limited to the pandemic  
314 period reported similar results: COVID-19 had an adjusted OR of 1.10 (95%CI 0.79 to  
315 1.52) for the risk of PE (Suppl table 2). Another sensitivity analysis after excluding the  
316 59 isolated sub-segmental PEs reported that COVID-19 had an adjusted OR of 0.97  
317 95%CI=[0.74 – 1.26] for the risk of PEs.

318 The area under the receiving operator characteristics curve of D-dimer for the  
319 diagnosis of PE was 0.79 (95%CI 0.76 – 0.81) for the general population, and 0.81  
320 (95%CI 0.77 – 0.85) in COVID-19 patients (figure 2).

321 A total of 207 patients had a non-high clinical probability and D-dimer below the age-  
322 adjusted threshold, among whom 4 had a PE; one in a COVID-19 patient and three  
323 in non COVID-19 patients. The percentage of false negative for the RGS with age-  
324 adjusted threshold was respectively of 1.4% and 2.2%.

325 **Discussion**

326 In this multicenter retrospective study, we report that COVID-19 is not associated  
327 with increased risk of PE diagnosis among ED patients who underwent a CTPA. The  
328 risk of PE was of 15% in both groups, and the adjusted OR of COVID-19 for PE was  
329 1.01 (95% CI 0.81 to 1.27).

330 This result is in contrast to recent reports and case series that highlighted a higher  
331 risk of thrombo-embolism in COVID-19 patients.<sup>17,18</sup> In our study, we focused on ED  
332 patients, who are, by definition, at the beginning of the part of their hospitalized stage  
333 of disease. Recent reports suggested an increased risk of thrombo-embolic events in  
334 admitted patients, both to wards and the intensive care unit. These patients may be  
335 at higher risk both because they were identified at a later stage of the disease, and  
336 also after a potential period of immobilization. Furthermore, these previous reports  
337 were not comparative, and therefore no definitive conclusion of increased risk could  
338 be made. It is likely that COVID-19 is associated with higher risk of PE in the general  
339 population, but our reports suggest that this is not the case among ED patients with  
340 suspicion of PE. This is in line with studies including pregnant women, who in the  
341 general population are at increased risk of thrombo-embolic events. However, in ED  
342 patients with suspected PE, pregnancy was not reported to be associated with higher  
343 risk of PE.<sup>19</sup>

344 We included patients based on whether a CTPA was performed in the ED. This is  
345 because the diagnostic strategy to rule out PE in the ED is based on a Bayesian  
346 approach, where the work-up (especially regarding the order of a CTPA) depends on  
347 the pre-test probability, which is dependent on PE prevalence in the studied  
348 population. We conducted this study to assess if COVID-19 was associated with PE,  
349 because if confirmed, it could have led to a change in the diagnostic strategy. Our

350 results suggest that the current strategy may be safe during COVID-19 pandemic  
351 because the pre-test probability of PE does not seem to depend on the COVID-19  
352 status. Furthermore, only one 'low risk' (non-high RGS and D-dimer below age  
353 adjusted threshold) patient was diagnosed with a sub-segmental PE among COVID-  
354 19 patients. However, since we only included patients that had had a CTPA  
355 performed, it is possible some patients with a non-high RGS and low D-dimer had a  
356 PE missed in the ED because a CTPA was not ordered.



357 **Limitation**

358 This study has several limitations. Firstly, patients were included only if a CTPA was  
359 performed in the ED. This means that all patients that had a suspicion of PE and a  
360 negative D-dimer and a non-high clinical probability of PE were excluded. This  
361 inclusion bias limits our ability to conclude whether or not these results can apply to  
362 the whole ED population with suspicion of PE, and moreover to the general  
363 population. Among included patients, it is possible that some underwent a CTPA for  
364 an alternate diagnosis such as aortic dissection. After screening all CTPA performed  
365 during the study period, the local investigator sought in the patient's file whether the  
366 CTPA may have been performed outside a suspicion of PE and subsequently  
367 excluded him/her. However, we may have missed some CTPAs with no clear listed  
368 indication and have a subsequent inclusion bias. Furthermore, it is possible that  
369 during the COVID-19 pandemic, emergency physicians may have had a lower  
370 threshold for ordering a CTPA especially because COVID-19 has been reported to be  
371 associated to higher risk of PE, and also because a lung CT was often performed to  
372 diagnose COVID-19. However, the patient's baseline characteristic was similar  
373 between the two periods (Supplemental table ), and we found no period effect in the  
374 analysis (Supplemental table 2). Furthermore, the sensitivity analysis restricted to  
375 patients included in the pandemic period reported similar result, with no association  
376 between COVID-19 and risk of PE (Supplemental table 3). However, a bias may still  
377 exist since the potential risk of COVID-19 induced coagulopathy was not described at  
378 the beginning of the pandemic period but after a few weeks. This bias is limited  
379 because patients were included until april 10<sup>th</sup>, before physicians were aware of  
380 suspected COVID-19 induced coagulopathy. A sensitivity analysis with time forced in

381 the model as a categorical variables (weeks of inclusion) reports similar results with  
382 no effect of time (Supplemental table 4).

383 Second, defining the presence of COVID-19 in the ED may be difficult. We excluded  
384 105 patients in whom COVID-19 status could not have been determined, but it is  
385 possible that other patients were wrongly classified. The reported sensitivity for the  
386 diagnosis of COVID-19 of RT-PCR ranges from 71%to 98% and 93% to 97% for  
387 lung CT.<sup>20,21</sup> To mitigate this, in this study, patients were considered to have COVID-  
388 19 if one or the other of the tests was positive, which limited the risk of false  
389 negatives. In 38% of cases, the diagnosis of COVID-19 was only adjudicated on CT.  
390 This is in part caused by the limited availability of RT-PCR testing in France, and the  
391 longer turnaround time for RT-PCR results compared to CT. In these patients, the  
392 sub-optimal specificity of CT could have led to false positives, and radiologists  
393 exhibited moderate performances in differentiating COVID-19 pneumonia from other  
394 viral pneumonia on lung CT.<sup>22,23</sup> This limit is inherent to our design, and represents a  
395 classification bias. However, this can be seen as a challenge faced in the day to day  
396 clinical practice of emergency medicine and patients with a suspected COVID-19. In  
397 our study, sensitivity of RT-PCR was 84% and false negative rate was 23%, which is  
398 consistent with what has been reported in the literature.<sup>20</sup> However, we cannot  
399 exclude that some COVID-19 patients may have had both false negative PCR and  
400 false negative CT.

401 In addition, we found a center effect and investigated this.It transpired that French  
402 EDs was a protective factor for PE (adjusted OR 0.61, 95%CI 0.48 – 0.78), which  
403 suggest different practice patterns across countries. This may reflect the fact that  
404 heterogenous data sources were combined, especially in light of the fact that French  
405 EDs dominated the sample size. The multivariable model adjusted the results for this

406 association, but whether this could affect the external validity of our results is  
407 unknown.

408 Last, as a retrospective study, although the case record form was standardized, there  
409 was no monitoring of data collection methods in the 6 countries and 26 sites. This  
410 was mitigated by making the data required as pragmatic and minimal as possible to  
411 satisfy the primary objective.

412

### 413 **Conclusion**

414 In ED patients that had CTPA performed for suspected PE, COVID-19 was not  
415 associated with a higher risk of PE. These results suggest that conventional  
416 diagnostic strategies for PE in ED patients with suspected COVID-19 are safe.

417

419 **References**

420

421 1. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019  
422 in China. *New England Journal of Medicine* 2020;0(0):null.423 2. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies  
424 in Patients with Covid-19. *New England Journal of Medicine* 2020;0(0):e38.425 3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic  
426 complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;427 4. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory  
428 Distress Syndrome and Death in Patients With Coronavirus Disease 2019  
429 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020;430 5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult  
431 inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*  
432 2020;395(10229):1054–62.433 6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is  
434 associated with decreased mortality in severe coronavirus disease 2019 patients  
435 with coagulopathy. *J Thromb Haemost* 2020;436 7. Freund Y, Cachanado M, Aubry A, et al. Effect of the Pulmonary Embolism  
437 Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk  
438 Emergency Department Patients: The PROPER Randomized Clinical Trial.  
439 *JAMA* 2018;319(6):559–66.440 8. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to  
441 categorize patients probability of pulmonary embolism: increasing the models  
442 utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83(3):416–20.443 9. Le Gal G, Righini M, Roy P-M, et al. Prediction of pulmonary embolism in the  
444 emergency department: the revised Geneva score. *Ann Intern Med*  
445 2006;144(3):165–71.446 10. Hulle T van der, Cheung WY, Kooij S, et al. Simplified diagnostic management  
447 of suspected pulmonary embolism (the YEARS study): a prospective,  
448 multicentre, cohort study. *The Lancet* 2017;390(10091):289–97.449 11. Bernheim A, Mei X, Huang M, et al. Chest CT Findings in Coronavirus Disease-  
450 19 (COVID-19): Relationship to Duration of Infection. *Radiology*  
451 2020;200463.452 12. Jiang Y, Guo D, Li C, Chen T, Li R. High-resolution CT features of the COVID-  
453 19 infection in Nanchong City: Initial and follow-up changes among different  
454 clinical types. *Radiology of Infectious Diseases* [Internet] 2020 [cited 2020 Jun  
455 6]; Available from:  
456 <http://www.sciencedirect.com/science/article/pii/S2352621120300474>

- 457 13. Li K, Fang Y, Li W, et al. CT image visual quantitative evaluation and clinical  
458 classification of coronavirus disease (COVID-19). *Eur Radiol* 2020;
- 459 14. Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America  
460 Expert Consensus Statement on Reporting Chest CT Findings  
461 Related to COVID-19. Endorsed by the Society of Thoracic  
462 Radiology, the American College of Radiology, and RSNA. *Radiology:  
463 Cardiothoracic Imaging* 2020;2(2):e200152.
- 464 15. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to  
465 rule out pulmonary embolism: the ADJUST-PE study. *JAMA*  
466 2014;311(11):1117–24.
- 467 16. Klok FA, Mos ICM, Nijkeuter M, et al. Simplification of the Revised Geneva  
468 Score for Assessing Clinical Probability of Pulmonary Embolism. *Arch Intern  
469 Med* 2008;168(19):2131–6.
- 470 17. Poissy Julien, Goutay Julien, Caplan Morgan, et al. Pulmonary Embolism in  
471 COVID-19 Patients: Awareness of an Increased Prevalence. *Circulation*  
472 [Internet] [cited 2020 Apr 26];0(0). Available from:  
473 <https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.120.047430>
- 474 18. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary  
475 Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT  
476 Angiography. *Radiology* 2020;201544.
- 477 19. Kline JA, Richardson DM, Than MP, Penaloza A, Roy P-M. Systematic review  
478 and meta-analysis of pregnant patients investigated for suspected pulmonary  
479 embolism in the emergency department. *Acad Emerg Med* 2014;21(9):949–59.
- 480 20. Watson J, Whiting PF, Brush JE. Interpreting a covid-19 test result. *BMJ*  
481 [Internet] 2020 [cited 2020 Jun 2];369. Available from:  
482 <https://www.bmj.com/content/369/bmj.m1808>
- 483 21. Adams HJA, Kwee TC, Yakar D, Hope MD, Kwee RM. Systematic Review and  
484 Meta-Analysis on the Value of Chest CT in the Diagnosis of Coronavirus  
485 Disease (COVID-19): *Sol Scientiae, Illustra Nos. AJR Am J Roentgenol* 2020;1–  
486 9.
- 487 22. Bai HX, Hsieh B, Xiong Z, et al. Performance of radiologists in differentiating  
488 COVID-19 from viral pneumonia on chest CT. *Radiology*  
489 2020;200823.
- 490 23. Kim H, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse  
491 Transcriptase-Polymerase Chain Reaction for Coronavirus Disease  
492 2019: A Meta-Analysis. *Radiology* 2020;201343.

493  
494

495  
496  
497  
498  
499  
500  
501  
502

**Figure 1:** Flow diagram. PE: pulmonary Embolism.

**Figure 2:** Receiving operator characteristic curves of D-dimer for diagnosis of pulmonary embolism in the emergency department.

A) whole population: area under the curve = 0.79, 95%CI=[0.76 ; 0.81]

B) COVID-19 patients: area under the curve = 0.81, 95%CI=[0.77 ; 0.85]

503

504

**Variable**

Age > 65 years	1
Previous DVT or PE	1
Surgery or immobilisation within 1 month	1
Active malignant condition	1
Clinical signs of DVT	2
Heart rate, beats/min	
75-94	1
≥ 95	1

505

506

507

508

509

510

511

512

**Table 1:** Simplified revised Geneva score. DVT: deep venous thrombosis. PE: pulmonary embolism. Score ranges from 0 to 8. High probability defined by a score > 4. From the original score, “unilateral lower-limb pain” and “pain on lower-limb deep venous palpation and unilateral edema” were merged as “clinical signs of deep venous thrombosis”, with a weigh of 2 points.

Variable	n	PE n=500	No PE n=2753
<b>Age (years), mean (SD)</b>			
<b>Sex</b>			
Female	3253	234 (45%)	1471 (53%)
<b>ED from France</b>	3253	358 (72%)	2276 (83%)
<b>Post pandemic period</b>	3253	252 (50%)	1642 (51%)
<b>Comorbidities</b>			
Chronic respiratory insufficiency	3248	42 (8%)	276 (10%)
Hypertension	3247	207 (42%)	1087 (40%)
Chronic heart failure	3248	61 (12%)	476 (17%)
Chronic kidney failure	3245	26 (5%)	133 (5%)
<b>ED presentation</b>			
Chest pain	3245	179 (36%)	1075 (39%)
Shortness of breath	3249	349 (70%)	1731 (63%)
Syncope	3245	60 (12%)	384 (14%)
Delay from onset to ED visit, median (IQR)	2883	3 [1; 7]	3 [1;7]
Heart rate (/min) , mean (SD)	2893	97 (20)	93 (20)
Respiratory Rate (/min), mean (SD)	2297	23 (7)	23 (7)
SpO2 (%), median [IQR]	3104	96 [93; 98]	97 [94; 99]
Systolic blood pressure, mean (SD)	3191	134 (24)	137 (24)
Temperature (°C), mean (SD)	3123	36.8 (0.8)	37 (0.9)
<b>Risk factors for PE</b>			
Estrogen use	3236	12 (2%)	78 (3%)
Clinical signs of DVT	3247	101 (11%)	248 (9%)
Surgery or trauma requiring immobilisation within 1 month	3246	53 (11%)	168 (6%)
Past history of PE or DVT	3245	106 (21%)	279 (10%)
Hemoptysis	3245	15 (3%)	104 (4%)
Active malignancy	3246	68 (14%)	374 (14%)
<b>Laboratory results</b>			
D-dimer (ng/ml), median (IQR)	2495	4270 [1730; 10000]	1181 [762; 2105]
Leucocytes, mean (SD)	3106	10.6 (4.6)	9.1 (5.1)
C-reactive protein, median (IQR)	2758	23 [7; 83]	14 [4; 65]

513

514 **Table 2: Baseline characteristics.** ED: emergency department SD: standard  
515 deviation. IQR: Interquartile range. PE: pulmonary embolism. DVT: deep venous  
516 thrombosis

517



		<b>PE</b> <b>n=500</b>	<b>No PE</b> <b>n=2753</b>
<b>Signs of COVID-19</b>			
		82 (16%)	470 (17%)
		54 (11%)	296 (11%)
		364 (73%)	1987 (72%)
<b>Extent of lesions</b>	<b>n=127</b>		<b>n=711</b>
		35 (28%)	197 (28%)
		47 (37%)	238 (33%)
		40 (31%)	255 (36%)
		5 (4%)	21 (3%)
<b>RT-PCR COVID-19</b>			
		202 (40%)	1136 (41%)
		80 (16%)	524 (19%)
<b>Confirmed COVID-19</b>		148 (30%)	826 (30%)

518

519

520

521

522

523

**Table 3:** COVID-19 status. PE: pulmonary embolism. RT-PCR: reverse transcriptase polymerase chain reaction. Extent of lesions: Moderate < 25%, extended 25-50%, Severe 50-75% and Critical >75%.

Variable	Bivariate		Multivariate	
	OR [95%CI]	p-value	OR [95%CI]	p-value
<b>Covid-19</b>	0.95 [0.77 – 1.18]	0.66	0.98 [0.76 – 1.26]	0.86
<b>Sexe male</b>	1.34 [1.10 – 1.62]	<b>0.0035</b>	1.46 [1.18 – 1.80]	<b>0.0005</b>
<b>Age (quartile)</b>		<b>0.0033</b>		<b>0.0186</b>
[75 – 103]	1.70 [1.28 – 2.25]		1.63 [1.20 – 2.21]	
[63 – 75[	1.43 [1.07 – 1.92]		1.38 [1.01 – 1.89]	
[48 – 63[	1.45 [1.08 – 1.94]		1.33 [0.98 – 1.81]	
[18 – 48[	1		1	
<b>Heart rate (bpm)</b>	1.01 [1.00 – 1.01]	<b>0.0007</b>	1.01 [1.01 – 1.02]	<b>&lt;0.0001</b>
<b>Past thrombo-embolic event</b>	2.41 [1.87 – 3.10]	<b>&lt;0.0001</b>	2.32 [1.77 – 3.04]	<b>&lt;0.0001</b>
<b>Hemoptysis</b>	0.81 [0.47 – 1.41]	0.46	0.84 [0.48 – 1.50]	0.56
<b>Clinical sign of DVT</b>	2.53 [1.95 – 3.28]	<b>&lt;0.0001</b>	2.31 [1.73 – 3.08]	<b>&lt;0.0001</b>
<b>Recent immobilisation</b>	1.93 [1.39 – 2.68]	<b>&lt;0.0001</b>	1.92 [1.34 – 2.75]	<b>0.0004</b>
<b>Active cancer</b>	1.97 [0.73 – 1.30]	0.85	0.76 [0.56 – 1.05]	0.09

524  
525 **Table 4:** Univariate and multivariable analysis, adjusted for center effect ( $p < 0.001$ )  
526 Age according to quartile. DVT: deep venous thrombosis. ED: emergency  
527 department. Overall classification rate (precision of the model): 69%, Hosmer  
528 Lemeshow p value: 0.4.  
529 Severity of CT lesion and pandemic period were not associated with PE ( $p = 0.72$  and  
530  $p = 0.54$  respectively).  
531