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## **Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with respiratory symptoms: A nested case-control study**

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1 **Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with**  
2 **respiratory symptoms: a nested case-control study.**

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46 **Abstract**

47 **Introduction.** Coronavirus disease 2019 (COVID-19) has been associated with  
48 cardiovascular complications and coagulation disorders. Previous studies reported pulmonary  
49 embolism (PE) in severe COVID-19 patients. Aim of the study was to estimate the prevalence  
50 of symptomatic PE in COVID-19 patients and to identify the clinical, radiological or  
51 biological characteristics associated with PE

52 **Patients/Methods.** We conducted a retrospective nested case-control study in 2 French  
53 hospitals. Controls were matched in a 1:2 ratio on the basis of age, sex and center. PE patients  
54 with COVID-19 were compared to patients in whom PE was ruled out (CTPA controls) and  
55 in whom PE has not been investigated (CT controls).

56 **Results.** PE was suspected in 269 patients among 1042 COVID-19 patients, and confirmed in  
57 59 patients (5.6%). Half of PE was diagnosed at COVID-19 diagnosis. PE patients did not  
58 differ from CT and CTPA controls for thrombosis risk factors. PE patients more often  
59 required invasive ventilation compared to CTPA controls (odds ratio (OR) 2.79; 95%  
60 confidence interval (CI) 1.33–5.84) and to CT controls (OR 8.07; 95% CI 2.70–23.82). PE  
61 patients exhibited more extensive parenchymal lesions (>50%) than CT controls (OR 3.90;  
62 95% CI 1.54–9.94). D-dimer levels were 5.1 (95% CI 1.90–13.76) times higher in PE patients  
63 than CTPA controls.

64 **Conclusions.** Our results suggest a PE prevalence in COVID-19 patients close to 5% in the  
65 whole population and to 20% of the clinically suspected population. PE seems to be  
66 associated with more extensive lung damage and to require more frequently invasive  
67 ventilation.

68 **Key words**

69 Pulmonary embolism, COVID-19, CTPA, D-dimer

70 Word count: 2901

71 Tables: 3

## 72 **Introduction**

73 In December 2019, China reported the first cluster of severe acute respiratory syndrome due  
74 to a new coronavirus (SARS-CoV-2).<sup>1</sup> The disease rapidly spread into a global pandemic of  
75 public health worldwide leading to more than 617 000 deaths (data from July 22, 2020). The  
76 main failure in COVID-19 was atypical acute respiratory distress syndrome (ARDS) because  
77 of the dissociation between well-conserved lung compliance and severe hypoxemia, attributed  
78 to pulmonary vasoregulation disruption and local thrombogenesis.<sup>2,3</sup> Furthermore, COVID-19  
79 outbreak coagulopathy has been described with unusual high levels of D-dimer in a large  
80 majority of patients<sup>1,4-6</sup>. High D-dimer levels, caused by both inflammation storm and  
81 coagulation activation have been associated with increased mortality.<sup>4,5,7-9</sup> Taking together,  
82 these reports have led to several therapeutic proposals in terms of anticoagulant therapy from  
83 scientific societies.<sup>10-12</sup> Publications recently reported thrombotic complications in series of  
84 severe COVID-19 patients admitted in intensive care unit (ICU), but the frequency of  
85 pulmonary embolism (PE) remains uncertain.<sup>13-20</sup>

86 Earlier during the European COVID-19 outbreak, the European Society of Radiology and the  
87 European Society of Thoracic Imaging suggested to performed CT-scan in COVID-19  
88 patients with respiratory symptoms such as dyspnea and desaturation<sup>21</sup>. Additional  
89 pulmonary CT angiogram (CTPA) could be performed if COVID-19 patient has symptoms  
90 susceptible to be associated with PE such as worsening of oxygen requirement and occurrence  
91 of ARDS. Hence, a nested-case control seems an appropriate methodology to compare PE  
92 patients to all COVID-19 in-patients with CT-scan requiring or not CTPA.

93 In the present analysis, we aimed to 1) evaluate the prevalence of PE among a large  
94 population of all consecutive patients admitted for COVID-19 pneumonia in two centers and  
95 2) identify the characteristics associated with PE in those patients by using a nested case-

96 control design with patients who underwent either unenhanced computed tomography (CT) or  
97 computed tomography pulmonary angiogram (CTPA).

98



99 **Methods**

100 **Patients and study design**

101 We conducted a retrospective study that included, from March 1 to April 20, 2020, all  
102 consecutive patients with COVID-19 pneumonia who had a CT scan for diagnosis and/or  
103 evaluation of the severity of lung lesions. All patients were recorded in a database in two  
104 large university hospitals in Paris, France: Groupe Hospitalier Paris Saint-Joseph (GHPSJ)  
105 and Hôpital Européen Georges Pompidou (HEGP).

106 Patients were included according to the following inclusion criteria: patients over 18 years of  
107 age, admitted for acute COVID-19 pneumonia and who underwent a chest CT at baseline for  
108 rapid triage assessment at the emergency room and/or in wards during their hospitalization.  
109 Diagnosis of SARS-CoV-2 infection was confirmed by a positive result of a reverse-  
110 transcriptase–polymerase-chain-reaction (RT-PCR) assay and/or typical CT findings of  
111 COVID-19 pneumonia. Exclusion criteria were patient’s refusal to participate and respiratory  
112 distress syndrome explained by another cause.

113 Patients were hospitalized in medical wards or ICU, if required, to receive usual supportive  
114 care including oxygen therapy, antibiotics, as well as prophylactic anticoagulation by low-  
115 molecular weight heparin (enoxaparin 4000 IU) or unfractionated heparin in case of  
116 glomerular filtration rate <30 mL/min.

117 From this COVID-19 cohort, we selected case patients with CTPA proven PE, and we  
118 compared them to two subgroups of controls matched for age, sex and center, in whom PE  
119 had been either excluded or not suspected: 1) COVID-19 patients with a negative CTPA  
120 (CTPA controls) and 2) COVID-19 patients with unenhanced CT only (CT controls). For  
121 more detailed methods for imaging protocol, see supplementary data.

122 The study sponsor is GHPSJ. The cohort protocol has been approved by the institutional  
123 ethics committee (IRB number IRB00012157 and registered on national institute of health  
124 data platform INDS n° MR 4516150520). The patients' non-opposition to the use of their data  
125 for research was also collected in accordance with European regulations (General Data  
126 Protection Regulation, GDPR). We followed requirement of the STROBE statement, on  
127 observational studies in epidemiology (<https://www.strobe-statement.org>).

### 128 **Clinical and laboratory data**

129 All data were extracted from our computed medical record (Dx-Care® MEDASYS, France)  
130 by distinct investigators independently. All data were confidentially collected and coded  
131 according to the local cohort IRB-approved statements. The database was frozen for statistical  
132 analysis on May 20, 2020. The computed file used for this research was implemented in  
133 accordance with French regulations and European regulations (GDPR). Demographic and  
134 medical characteristics, including age, sex, body mass index (BMI), history of venous or  
135 arterial thrombosis, tobacco use, and anticoagulant treatment at admission and before the  
136 diagnosis of PE were available in medical records. During follow-up, maximal oxygen flow  
137 required or the need of invasive mechanical ventilation (IMV) were recorded. Time from  
138 COVID-19 illness onset to hospital admission and to PE diagnosis have been recorded.  
139 Patients status at the end of the inclusion period was recorded as discharged from hospital,  
140 still hospitalized or deceased.

141 Biological parameters at admission including complete blood count, aspartate and alanine  
142 aminotransferase (ASAT, ALAT), plasma creatinine were recorded. We report D-dimer  
143 values in PE patients and CTPA controls, using the STA®-Liatest® D-Di (Diagnostica Stago,  
144 Asnières, France) (GHPSJ) or the Vidas D-Dimer® assay (Biomérieux, Marcy-Etoile, France)  
145 (HEGP). During follow-up, highest values of C-reactive protein (CRP) and fibrinogen were

146 also noted. Nasopharyngeal swabs were collected in universal transport medium (Xpert®  
147 nasopharyngeal sample collection kit) at hospital admission. SARS CoV-2 was detected using  
148 Allplex™ 2019-nCoV Assay (Seegene), a multiplex Real-time PCR assay that detects three  
149 target genes (E gene, RdRP gene and N gene) in a single tube, as previously described.<sup>22</sup> Only  
150 qualitative data were available.

## 151 **Study outcomes**

152 The main purpose of our study was to estimate the prevalence of symptomatic PE in a large  
153 population of consecutive COVID-19 patients presenting with respiratory symptoms.  
154 Secondary objectives were to identify the clinical, radiological or biological characteristics  
155 associated with PE. We also analyzed whether or not PE was associated with a worse  
156 outcome in hospitalized COVID-19 patients. Finally, we evaluated the diagnostic  
157 performance of D-dimer for the diagnosis of PE in COVID-19 patients.

## 158 **Statistical analysis**

159 Cases and controls were matched in a 1:2 ratio on the basis of age, sex and center. For each  
160 patient of the PE group, a greedy-matching algorithm was used to select the control patients  
161 who most closely matched that patient in terms of the three matching factors.<sup>23</sup> This resulted  
162 in 2 different case-control studies. The first one compares the PE group to a control group  
163 sampled in the whole database of COVID-19 patients who had a CTPA and did not have PE  
164 (CTPA controls). The second one compares the PE group to a control group sampled in the  
165 whole database of COVID-19 patients who had an unenhanced CT-scan (CT controls).

166 Categorical variables are presented as number of patients (percentages) and quantitative  
167 variables as median (interquartile range [IQR]). All percentages were calculated for available  
168 data for each variable. Unadjusted conditional logistic regression analysis, which accounted  
169 for the matched study design, was performed to evaluate the association of various clinical or

170 biological characteristics with the risk of having PE. Odds ratios (OR) are displayed with their  
171 95% confidence intervals (CI). To evaluate the diagnostic performance of D-dimer in  
172 predicting PE, receiver operating characteristic (ROC) curve analysis of D-dimer  
173 concentration prior to CTPA evaluation was performed. Youden's index (calculated as  
174 sensitivity + specificity – 1) was chosen to obtain the optimal D-dimer threshold. Sensitivity  
175 and specificity are calculated with standard formulas. The positive and negative predictive  
176 values (PPV and NPV) were calculated with the Bayes' theorem with the PE prevalence  
177 obtained in the whole cohort (5.6%) and in the cohort with CTPA (21.2%). Statistical  
178 analyses were performed using the NCSS 2020 statistical software.

179 **Results**

180 **Population**

181 This study included a total of 1042 COVID-19 patients assessed by at least one chest CT scan  
182 for respiratory symptoms (454 in GHPSJ and 588 in HEGP). During the same period 115 and  
183 102 COVID-19 patients were hospitalized in GHPSJ and HEGP without CT or CTPA,  
184 respectively. *Among the whole 1259 COVID-19 patients, 312 (24.7%) required ICU.* The  
185 median age of the population was 63 years (53–79) and 59.8% were male. Among the 1042  
186 COVID-19 patients, CTPA was performed in 269 (25.8%) patients for PE suspicion; 59  
187 patients were diagnosed with PE (27 in GHPSJ and 32 in HEGP). The prevalence of PE in  
188 this entire COVID-19 population was 5.6%. By considering only the group of 269 patients  
189 who underwent CTPA, the prevalence of PE was 21.2%.

190 Median time from onset of reported COVID-19 symptoms and PE diagnosis was 15 days.  
191 Twenty-eight (47.5%) PE were diagnosed on the day of admission. In 36 patients (61.0%) PE  
192 was suspected because of increasing oxygen requirements, in 16 (27.1%) patients because of  
193 PE symptoms such as chest pain, tachycardia or right cardiac failure and in 6 (10.2%) patients  
194 because initial symptoms could not be explained by the lung parenchymal findings alone. One  
195 PE was an incidental finding. History of venous thrombosis was present in 5 (8.6%) patients.  
196 Active smoking was found in only 2 (3.4%) patients. Locations of the emboli were proximal  
197 (pulmonary trunk or lobar artery) in 27 (45.7%) patients, segmental in 24 (40.6%) patients  
198 and sub-segmental in 8 (13.6%) patients. At PE diagnosis, 32 (54.2%) patients had received  
199 anticoagulant at prophylactic dose (at least one dose) and 4 (6.9%) patients at therapeutic  
200 dose. Among these 59 PE patients, 25 (42.4%) were treated by IMV in ICU corresponding to  
201 a PE prevalence in ICU of 8.0%

202

203 **Clinical characteristics**

204 The main clinical characteristics of PE patients and matched CTPA and CT controls are  
205 summarized in Table 1. BMI, history of venous or arterial thrombosis, were not associated  
206 with the occurrence of PE in this population. Interestingly, active smoking was uncommon in  
207 this COVID-19 population and was not associated with the occurrence of PE. Therapeutic  
208 anticoagulation and hydroxychloroquine treatment were not associated with a decreased risk  
209 of PE.

210 IMV was associated with an increased risk of PE with an OR of 2.79 (95% CI 1.33–5.84)  
211 compared to CTPA controls and with an OR of 8.07 (95% CI 2.70–23.82) compared to CT  
212 controls. Twelve deaths (20.3%) occurred in PE patients, as compared to 19 (16.1%) in CTPA  
213 controls (OR 1.36; 95% CI 0.53–3.14) and 14 (11.9%) in CT controls (OR 2.09; 95% CI  
214 0.83–5.31). Only one death out of 12 was directly linked to a high risk PE in a 41 year-old  
215 woman. Excluding deceased patients, median length of hospital stay was not significantly  
216 higher in PE patients as compared to either control groups.

217

218 **Radiological and biological characteristics**

219 The main radiological and biological characteristics of the cases and controls are summarized  
220 in Table 2. There was no difference between PE patients and the two control groups in terms  
221 of CT findings suggestibility for COVID-19 on the first CT scan, with highly suggestive  
222 features found in a majority of patients in all groups. PE patients exhibited more extensive  
223 lesions than the CT controls (OR 3.9; 95% CI 1.54–9.94, for a parenchymal involvement  
224 >50%). At admission, there was no difference among PE patients and the two control groups  
225 regarding hemoglobin level, platelet count, lymphocyte count, creatinine, ASAT and ALAT  
226 levels. Regarding inflammation during the hospitalization, assessed by both CRP and

227 fibrinogen, PE diagnosis tends to be associated with increased levels of these biomarkers. The  
228 risk of PE was significantly associated with CRP elevation (OR 3.36; 95% CI 1.58–7.14)  
229 compared to CT controls.

230

### 231 **D-dimer level**

232 Among COVID-19 patients with suspected PE, the risk of being diagnosed with PE was 5.11  
233 times higher in patients with D-dimer level above 2605 ng/mL (95% CI 1.90–13.76). The  
234 ROC curve for D-dimer as a predictive marker for PE is shown in Supplemental figure 1.  
235 According to the Youden index, the optimal D-dimer level cut-off was 1500 ng/mL (Table 3).  
236 The sensitivity of the test is 76.1% and the specificity is 65.0%. With this test, in our  
237 population, the NPV was 97.8% and 91.1% according to a PE prevalence of 5.6% (whole  
238 population) or 21.2% (population with CTPA). On the other hand, we also assessed if a higher  
239 threshold of D-dimer would have a good PPV for the diagnosis of PE. In our population of  
240 1042 COVID-19 patients, thresholds of 2500 ng/mL and 3500 ng/mL, were associated with a  
241 PPV of 15.9% and 20.3% respectively. In the suspected PE group (CTPA group), PPV were  
242 of 45.4% and 53.3% respectively.

## 243 **Discussion**

244 Our study evaluates the prevalence of PE in 1042 COVID-19 patients consecutively admitted  
245 in 2 large French hospitals for acute respiratory symptoms, during the main period of the  
246 pandemic in France. We found a prevalence of PE of 5.6% in this large population. This rate  
247 could be considered as a high prevalence of PE in such unselected population. Considering  
248 that 24.7% of patients required ICU, our study highlight that PE prevalence is 3 times higher  
249 than the 1.7% prevalence observed in the ICU population of the PROTECT study (dalteparin  
250 versus unfractionated heparin prophylaxis of thromboembolism in critical care) that included  
251 60% of patients for respiratory or sepsis conditions.<sup>24</sup> In a study of 198 consecutive Dutch  
252 patients a similar prevalence of PE was observed (6.6%)<sup>17</sup> and a prevalence of 2.8% in 388  
253 Italian patients.<sup>18</sup> Recently a French multicentric study found a prevalence of 8.3% in large  
254 population of COVID-19 patients hospitalized in medical wards<sup>20</sup>.

255 Furthermore, compared to recent prevention studies in acutely ill medical patients, the  
256 prevalence of PE in our population is 10 times higher than the prevalence observed in these  
257 randomized trials, demonstrating the high thrombotic risk associated with COVID-19.<sup>25-28</sup>  
258 Nevertheless, it remains difficult to draw definite conclusions by comparing incidence  
259 measured in randomized studies in ICU to prevalence observed in our retrospective series. In  
260 COVID-19 patients who had CTPA performed, we found a PE prevalence of 21.2%.  
261 Recently, 4 studies of less than 200 COVID-19 patients, mainly hospitalized in ICU, found a  
262 similar prevalence of PE between 13.5% and 30%.<sup>14-17</sup> Interestingly, almost half of the PE  
263 episodes were diagnosed at hospital admission as previously described<sup>18</sup>, suggesting that PE  
264 should be suspected at COVID-19 diagnosis in patients with respiratory symptoms.  
265 Furthermore, for hospitalized patients PE occurred despite the fact that patients received  
266 prophylactic anticoagulation, either with regular or higher doses, as physicians were aware of  
267 the higher thrombotic risk in this population. The protective effect of hydroxychloroquine on



268 thrombotic events in systemic lupus erythematosus was not observed in our COVID-19  
269 population.<sup>29</sup>

270 We did not find a higher prevalence for VTE risk factors in PE patients compared to both  
271 control groups. IMV was strongly associated with the occurrence of PE, compared to both  
272 control groups. The association remains true considering high flow oxygen therapy ( $\geq 6$   
273 L/min) compared to lower flow oxygen therapy. Therefore, PE patients seemed more severe  
274 than controls.

275 Interestingly and in accordance with another report<sup>30</sup>, the mortality did not differ between  
276 groups suggesting that PE does not impact patient's survival in this COVID-19 population.

277 Patients with PE tended to have a higher CRP than patients in the 2 control groups and to  
278 present more extensive COVID-19 lung damages. Those findings have been related to a more  
279 severe COVID-19 associated coagulopathy.<sup>10</sup> Two other French studies showed that PE was  
280 more frequent in ICU COVID-19 patients when compared to ARDS non-COVID-19  
281 patients<sup>16</sup> or patients with influenza infection.<sup>14</sup> Finally, our data are concordant with the  
282 hypothesis of a specific effect of the SARS-CoV-2 infection in thrombosis and inflammation.

283 A recent autopsy study demonstrated a high incidence of thromboembolic events associated  
284 with COVID-19 coagulopathy (58%), but histology also demonstrated microvascular  
285 thrombosis.<sup>31</sup> Clinical and pathology studies demonstrated endothelial injury<sup>32</sup> associated with  
286 intracellular SARS-CoV-2 infection, widespread microangiopathy of alveolar capillaries and  
287 angiogenesis, features that appeared different from influenza A (H1N1) infection.<sup>33</sup>  
288 Furthermore, recently, our team showed that therapeutic anticoagulation at admission could  
289 prevent COVID-19-associated endothelial injury.<sup>6</sup>

290 Previous reports<sup>1,4,8,7,5,6</sup> have shown that D-dimer levels are increased during COVID-19-  
291 associated coagulopathy and higher D-dimer levels at admission are associated with VTE

292 during follow-up.<sup>17</sup> The use of high D-dimer thresholds, such as 3500 ng/mL, is not effective  
293 enough to diagnose PE or initiate therapeutic anticoagulation, as we showed that the D-dimer  
294 positive predictive value in patients with suspected PE was only 50%. As previously  
295 published D-dimer are increased in pneumonia and associated with radiologic pneumonia  
296 extension<sup>34</sup> Furthermore, in patients diagnosed with community-acquired pneumonia, D-  
297 dimers were more elevated in patients with high probability PE<sup>35</sup>.

298 Our study results suggest that D-dimer measurement has a poor performance for PE diagnosis  
299 that should be only driven by CTPA or V/Q lung scan use as suggested by the recent ISTH  
300 guidance<sup>36</sup>. The main limitation of this strategy is the prevalence of renal impairment<sup>37</sup> and  
301 the risk of contrast-induced nephropathy in COVID-19 patients especially in ICU.  
302 Considering that PE could be frequently suspected at COVID-19 diagnosis or when  
303 respiratory condition gets worse, majority of patients would require CTPA. A specific clinical  
304 probability score, a specific D-dimer threshold or an adjusted strategy pending damage lung  
305 extent could help in reducing CTPA use in COVID-19 patients

306 Our study has a few limitations. First this is a retrospective series due to the emergency of the  
307 health crisis. Second outcomes analysis may be biased because some patients were still  
308 hospitalized at the time of data collection and other patients were transferred to other  
309 hospitals. Thus, it may lead to immortal time bias, potentially affecting the PE prevalence.  
310 Finally, screening for PE is mainly dependent on the decision to perform CTPA i.e. for  
311 clinical suspicion of PE and in patients with worsening of oxygen dependence or acute  
312 degradation of hemodynamic status. But, as the practice of CTPA investigations was not pre-  
313 defined according to specific criteria but left to the appreciations of the different clinicians in  
314 charge of the patients; obviously more severe patients received CTPA. To circumvent this  
315 potential limitation, we performed a nested case-control study in our large population of 1042

316 patients with COVID-19 acute respiratory syndrome. On the contrary, the fact that only one  
317 quarter of the studied population had a CTPA probably underestimates the rate of PE.

318 **Conclusion**

319 Our study results suggest a PE prevalence in COVID-19 patients close to 5% in the whole  
320 population and to 20% of the clinically suspected population. D-dimer could be an interesting  
321 tool in the diagnostic strategy of PE as long as the threshold is adjusted to the COVID-19  
322 associated coagulopathy. Further prospective studies are necessary to confirm the thresholds  
323 of D-dimer analyzed here, and to alert physicians on the high risk of PE in this setting.

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435 **Table 1. Clinical characteristics of the COVID-19 study patients**

| Characteristic                                      | PE patients<br>(n = 59) | CTPA controls<br>(n = 118) | CT controls<br>(n = 118) | OR (95% CI) <sup>a</sup> | OR (95% CI) <sup>b</sup> |
|---|-------------------------|----------------------------|--------------------------|--------------------------|--------------------------|
| Age (years)   | 63 (53–79)              | 65 (54–78)                 | 63 (53–78)               | –                        | –                        |
| Male  | 33 (55.9)               | 68 (58.1)                  | 66 (55.9)                | –                        | –                        |
| BMI (kg/m <sup>2</sup> )                            | 27.8 (24.4–31.9)        | 26.6 (23.8–29.6)           | 25.1 (22.1–29.1)         | 1.39 (0.60–3.21)         | 1.66 (0.60–4.59)         |
| BMI ≥30 kg/m <sup>2</sup>                           | 16 (34.4)               | 20 (24.4)                  | 12 (10.2)                | 2.02 (0.84–4.90)         | 1.61 (0.64–4.05)         |
| History of venous thrombosis (PE/DVT)               | 5 (8.6)                 | 13 (11.2)                  | 7 (6.1)                  | 0.72 (0.23–2.26)         | 1.48 (0.44–4.95)         |
| Cancer  | 3 (5.1)                 | 16 (13.6)                  | 14 (12.0)                | 0.34 (0.01–1.23)         | 0.37 (0.10–1.40)         |
| History of arterial thrombosis                      | 6 (10.5)                | 22 (19.1)                  | 25 (22.3)                | 0.38 (0.12–1.17)         | 0.36 (0.13–1.02)         |
| Hypertension  | 22 (37.2)               | 54 (45.8)                  | 55 (46.6)                | 0.7 (0.35–1.39)          | 0.61 (0.28–1.31)         |
| Atrial fibrillation                                 | 2 (3.4)                 | 8 (6.8)                    | 9 (7.9)                  | 0.50 (0.11–2.35)         | 0.41 (0.09–2.02)         |
| Active smoking                                      | 2 (3.5)                 | 7 (6.6)                    | 11 (10.2)                | 0.52 (0.11–2.53)         | 0.32 (0.07–1.60)         |
| Time from illness onset to PE diagnosis (days)      | 15 (11–20)              | –                          | –                        | –                        | –                        |
| Time from admission to PE diagnosis (days)          | 1 (0–8)                 | –                          | –                        | –                        | –                        |
| <b>Oxygen–support category<sup>c</sup></b>          |                         |                            |                          |                          |                          |
| Invasive mechanical ventilation                     | 25 (42.4)               | 25 (24.0)                  | 12 (12.5)                | –                        | –                        |
| High–flow oxygen (≥6 L/min)                         | 16 (27.1)               | 33 (31.7)                  | 18 (18.8)                | –                        | –                        |
| Low–flow oxygen (<6 L/min) or room air              | 18 (30.5)               | 46 (44.3)                  | 66 (68.7)                | –                        | –                        |
| Invasive mechanical ventilation versus none         | –                       | –                          | –                        | 2.79 (1.33–5.84)         | 8.07 (2.73–23.82)        |
| High–flow oxygen versus Low–flow oxygen or room air | –                       | –                          | –                        | 1.46 (0.55–3.91)         | 2.91 (1.09–7.73)         |
| <b>Treatment</b>                                    |                         |                            |                          |                          |                          |

|   |           |           |           |                  |                  |
|---|-----------|-----------|-----------|------------------|------------------|
| Hydroxychloroquine <sup>d</sup>                       | 16 (28.1) | 33 (28.7) | 30 (26.8) | 0.97 (0.46–2.08) | 1.11 (0.46–2.66) |
| Prophylactic anticoagulation                          | 32 (55.2) | 39 (33.6) | 44 (39.6) | 0.38 (0.12–1.22) | 1.31 (0.31–5.57) |
| Therapeutic anticoagulation <sup>d</sup>              | 4 (6.9)   | 18 (15.5) | 6 (5.4)   | 0.39 (0.12–1.20) | 1.32 (0.31–5.57) |
| <b>Outcome</b>  |           |           |           |                  |                  |
| Hospital length of stay before discharge alive (days) | 12 (3–18) | 8 (2–15)  | 5 (2–10)  | 1.06 (0.32–3.44) | 2.00 (0.72–5.59) |
| Death   | 12 (20.3) | 19 (16.1) | 14 (11.9) | 1.36 (0.59–3.14) | 2.09 (0.83–5.31) |

436 Continuous parameters are reported as median (IQR) and data expressed as *n* (%). All percentages were calculated for available data for each  
437 variable. <sup>a</sup>PE patients versus CTPA controls; <sup>b</sup>PE patients versus CT controls; <sup>c</sup>Higher oxygen-support category during hospital stay. <sup>d</sup>before PE  
438 diagnosis in PE patients. BMI = body mass index; PE = pulmonary embolism; DVT deep vein thrombosis; CTPA = computed tomography  
439 pulmonary angiogram; CT = unenhanced computed tomography; OR = odds ratio.

440 **Table 2. Radiologic and biological characteristics of the COVID-19 study patients**

|  | <b>PE patients<br/>(n = 59)</b> | <b>CTPA controls<br/>(n = 118)</b> | <b>CT controls<br/>(n = 118)</b> | <b>OR (95% CI)<sup>a</sup></b> | <b>OR (95% CI)<sup>b</sup></b> |
|--|---------------------------------|------------------------------------|----------------------------------|--------------------------------|--------------------------------|
| <b>Radiologic characteristic</b>                             |                                 |                                    |                                  |                                |                                |
| <b>Findings of COVID-19 on the first chest CT performed</b>  |                                 |                                    |                                  |                                |                                |
| Non suggestive   | 4 (6.8)                         | 11 (9.3)                           | 7 (5.9)                          | ref                            | ref                            |
| Indeterminate  | 10 (16.9)                       | 40 (33.9)                          | 47 (39.8)                        | 0.79 (0.21–2.95)               | 0.30 (0.07–1.33)               |
| Highly suggestive  | 45 (76.3)                       | 67 (56.8)                          | 64 (54.3)                        | 3.33 (0.83–13.34)              | 1.41 (0.30–6.54)               |
| <b>Extent of lung damage on the first chest CT performed</b> |                                 |                                    |                                  |                                |                                |
| <10% (limited)   | 9 (15.2)                        | 19 (16.1)                          | 29 (24.6)                        | ref                            | ref                            |
| 10–50% (mild or moderate)                                    | 23 (39.0)                       | 66 (55.9)                          | 70 (59.3)                        | 0.78 (0.29–2.14)               | 1.07 (0.44–2.58)               |
| >50% (severe or diffuse)                                     | 27 (45.8)                       | 33 (28.0)                          | 19 (16.1)                        | 1.82 (0.63–5.23)               | 3.90 (1.54–9.94)               |
| <b>Location of PE</b>  |                                 |                                    |                                  |                                |                                |
| Pulmonary trunk  | 12 (20.0)                       | –                                  | –                                | –                              | –                              |
| Lobar artery   | 15 (25.5)                       | –                                  | –                                | –                              | –                              |
| Segmental artery   | 24 (41.0)                       | –                                  | –                                | –                              | –                              |
| Sub-segmental artery   | 8 (13.5)                        | –                                  | –                                | –                              | –                              |
| <b>Biological characteristic</b>                             |                                 |                                    |                                  |                                |                                |
| D-dimers <sup>c</sup> (ng/mL)                                | 2605 (1436–7333)                | 1237 (885–2075)                    | –                                | 5.11 (1.90–13.76)              | –                              |
| Fibrinogen <sup>d</sup> (g/L)                                | 6.6 (4.6–7.7)                   | 5.6 (4.9–7.0)                      | 5.45 (4.7–6.58)                  | 1.59 (0.71–3.55)               | 2.20 (0.87–5.57)               |
| CRP <sup>d</sup> (mg/L)                                      | 136 (56–244)                    | 100 (30–158)                       | 88 (25–131)                      | 1.66 (0.84–3.27)               | 3.36 (1.58–7.14)               |
| Hemoglobin <sup>e</sup> (g/dL)                               | 13.2 (11.9–14.2)                | 13.3 (11.8–14.4)                   | 13.3 (12.3–14.5)                 | 0.70 (0.35–1.39)               | 0.76 (0.40–1.43)               |
| Platelet count <sup>e</sup> (G/L)                            | 227 (175–310)                   | 213 (148–288)                      | 201 (160–257)                    | 1.27 (0.65–2.48)               | 1.36 (0.69–2.68)               |
| Lymphocyte count <sup>e</sup> (M/L)                          | 895 (697–1342)                  | 860 (597–1242)                     | 865 (662–1220)                   | 1.55 (0.80–2.99)               | 1.46 (0.67–3.16)               |
| Creatinine <sup>e</sup> (μmol/L)                             | 75 (60–90)                      | 77 (61–99)                         | 76 (61–94)                       | 0.77 (0.40–1.48)               | 0.86 (0.42–1.75)               |
| ASAT <sup>e</sup> (IU/L)                                     | 49 (33–79)                      | 48 (33–71)                         | 40 (28–57)                       | 1.15 (0.58–2.28)               | 1.71 (0.86–3.41)               |
| ALAT <sup>e</sup> (IU/L)                                     | 31 (22–59)                      | 30 (18–60)                         | 27 (17–49)                       | 1.20 (0.58–2.46)               | 1.42 (0.68–2.99)               |

441 Continuous parameters are reported as median (IQR) and data expressed as *n* (%). All percentages were calculated for available data for each  
442 variable. <sup>a</sup>PE patients versus CTPA controls; <sup>b</sup>PE patients versus CT controls; <sup>c</sup>before CTPA assessment. <sup>d</sup>higher level during hospitalisation.  
443 <sup>e</sup>level at admission PE = pulmonary embolism; CTPA = computed tomography pulmonary angiogram ; CT = unenhanced computed tomography;  
444 OR = odds ratio.

445 **Table 3. Sensitivity and specificity of several D-dimer thresholds in PE-diagnosis in**  
 446 **COVID-19 patients with respiratory symptoms.**

|   |                  |                 |              |           | <b>PE prevalence in COVID-19 patients<sup>a</sup></b> |            |              |            |            |
|---|------------------|-----------------|--------------|-----------|---|------------|--------------|------------|------------|
| <b>PE</b>   |                  |                 |              |           | <b>5.6%</b>   |            | <b>21.2%</b> |            |            |
| <b>D-dimer <math>\geq 500</math> ng/mL</b>              |                  |                 |              |           |   |            |              |            |            |
|   | <b>Confirmed</b> | <b>Excluded</b> | <b>Total</b> | <b>Se</b> | <b>Sp</b>   | <b>NPV</b> | <b>PPV</b>   | <b>NPV</b> | <b>PPV</b> |
| $\geq 500$  | 46               | 91              | 137          | 100.0     | 9.0   | 100.0      | 6.2          | 100.0      | 22.8       |
| $< 500$   | 0                | 9               | 9            |           |   |            |              |            |            |
| <b>Total</b>  | 46               | 100             | 146          |           |   |            |              |            |            |
| <b>D-dimer <math>\geq 1500</math> ng/mL<sup>b</sup></b> |                  |                 |              |           |   |            |              |            |            |
|   | <b>Confirmed</b> | <b>Excluded</b> | <b>Total</b> | <b>Se</b> | <b>Sp</b>   | <b>NPV</b> | <b>PPV</b>   | <b>NPV</b> | <b>PPV</b> |
| $\geq 1500$   | 35               | 35              | 70           | 76.1      | 65.0  | 97.8       | 11.6         | 91.1       | 36.6       |
| $< 1500$  | 11               | 65              | 76           |           |   |            |              |            |            |
| <b>Total</b>  | 46               | 100             | 146          |           |   |            |              |            |            |
| <b>D-dimer <math>\geq 2500</math> ng/mL</b>             |                  |                 |              |           |   |            |              |            |            |
|   | <b>Confirmed</b> | <b>Excluded</b> | <b>Total</b> | <b>Se</b> | <b>Sp</b>   | <b>NPV</b> | <b>PPV</b>   | <b>NPV</b> | <b>PPV</b> |
| $\geq 2500$   | 23               | 16              | 39           | 50.0      | 84.0  | 96.5       | 15.9         | 86.3       | 45.4       |
| $< 2500$  | 23               | 84              | 107          |           |   |            |              |            |            |
| <b>Total</b>  | 46               | 100             | 146          |           |   |            |              |            |            |
| <b>D-dimer <math>\geq 3500</math> ng/mL</b>             |                  |                 |              |           |   |            |              |            |            |
|   | <b>Confirmed</b> | <b>Excluded</b> | <b>Total</b> | <b>Se</b> | <b>Sp</b>   | <b>NPV</b> | <b>PPV</b>   | <b>NPV</b> | <b>PPV</b> |
| $\geq 3500$   | 20               | 10              | 30           | 43.5      | 90.0  | 96.4       | 20.3         | 85.6       | 53.3       |
| $< 3500$  | 26               | 90              | 116          |           |   |            |              |            |            |
| <b>Total</b>  | 46               | 100             | 146          |           |   |            |              |            |            |

447 <sup>a</sup>Two prevalences were tested considering prevalence of PE in our cohort (5.6%) and  
 448 prevalence of PE in patients for whom it has been suspected (21.2%); <sup>b</sup>Optimal D-dimer  
 449 according to the ROC curve. PE = pulmonary embolism; Se = sensitivity; Sp = specificity;  
 450 NPV = negative predictive value; PPV = positive predictive value.