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► To cite this version:

Benjamin Planquette, Alice Le Berre, Lina Khider, Alexandra Yannoutsos, Nicolas Gendron, et al.. Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with respiratory symptoms: A nested case-control study. *Thrombosis Research*, 2021, 197, pp.94 - 99. 10.1016/j.thromres.2020.11.001 . hal-03493066

HAL Id: hal-03493066

<https://hal.science/hal-03493066>

Submitted on 21 Nov 2022

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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).¹ 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.^{2,3} Furthermore, COVID-19
79 outbreak coagulopathy has been described with unusual high levels of D-dimer in a large
80 majority of patients^{1,4-6}. High D-dimer levels, caused by both inflammation storm and
81 coagulation activation have been associated with increased mortality.^{4,5,7-9} Taking together,
82 these reports have led to several therapeutic proposals in terms of anticoagulant therapy from
83 scientific societies.¹⁰⁻¹² 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.¹³⁻²⁰

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 desaturation²¹. 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.²² 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.²³ 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.²⁴ In a study of 198 consecutive Dutch
252 patients a similar prevalence of PE was observed (6.6%)¹⁷ and a prevalence of 2.8% in 388
253 Italian patients.¹⁸ Recently a French multicentric study found a prevalence of 8.3% in large
254 population of COVID-19 patients hospitalized in medical wards²⁰.

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-19.²⁵⁻²⁸
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%.¹⁴⁻¹⁷ Interestingly, almost half of the PE
263 episodes were diagnosed at hospital admission as previously described¹⁸, 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.²⁹

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 (≥ 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 report³⁰, 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.¹⁰ Two other French studies showed that PE was
280 more frequent in ICU COVID-19 patients when compared to ARDS non-COVID-19
281 patients¹⁶ or patients with influenza infection.¹⁴ 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.³¹ Clinical and pathology studies demonstrated endothelial injury³² 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.³³
288 Furthermore, recently, our team showed that therapeutic anticoagulation at admission could
289 prevent COVID-19-associated endothelial injury.⁶

290 Previous reports^{1,4,8,7,5,6} 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.¹⁷ 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 extension³⁴ Furthermore, in patients diagnosed with community-acquired pneumonia, D-
297 dimers were more elevated in patients with high probability PE³⁵.

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 guidance³⁶. The main limitation of this strategy is the prevalence of renal impairment³⁷ 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.

324 **Acknowledgements**

325 We would like to acknowledge all nurses, technicians and physicians involved in the Vascular
326 medicine, Radiology, Internal medicine, Respiratory medicine, Intensive care and
327 Hematology departments of GHPSJ and HEGP for their help in taking care of patients and
328 including them in the study. We thank Andréanne Durivage for the English editing.

329 **References.**

- 330 1 Guan W, Ni Z, Hu Y, *et al.* Clinical Characteristics of Coronavirus Disease 2019 in
331 China. *N Engl J Med* 2020; **382**: 1708–20.
- 332 2 Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA* 2020;
333 published online April 24. DOI:10.1001/jama.2020.6825.
- 334 3 Diehl J-L, Peron N, Chocron R, *et al.* Respiratory mechanics and gas exchanges in the
335 early course of COVID-19 ARDS: a hypothesis-generating study. *Ann Intensive Care*
336 2020; **10**: 95.
- 337 4 Zhou F, Yu T, Du R, *et al.* Clinical course and risk factors for mortality of adult
338 inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;
339 **395**: 1054–62.
- 340 5 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with
341 poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;
342 **18**: 844–7.
- 343 6 Khider L, Gendron N, Goudot G, *et al.* Curative anticoagulation prevents endothelial
344 lesion in COVID-19 patients. *J Thromb Haemost JTH* 2020; published online June 18.
345 DOI:10.1111/jth.14968.
- 346 7 Wang D, Hu B, Hu C, *et al.* Clinical Characteristics of 138 Hospitalized Patients With
347 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061.
- 348 8 Chen T, Wu D, Chen H, *et al.* Clinical characteristics of 113 deceased patients with
349 coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091.
- 350 9 Han H, Yang L, Liu R, *et al.* Prominent changes in blood coagulation of patients with
351 SARS-CoV-2 infection. *Clin Chem Lab Med* 2020; **58**: 1116–20.
- 352 10 Thachil J, Tang N, Gando S, *et al.* ISTH interim guidance on recognition and
353 management of coagulopathy in COVID-19. *J Thromb Haemost* 2020; **18**: 1023–6.
- 354 11 Bikdeli B, Madhavan MV, Jimenez D, *et al.* COVID-19 and Thrombotic or
355 Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and
356 Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; **75**: 2950–73.
- 357 12 Khider L, Soudet S, Laneelle D, *et al.* Proposal of the French Society of Vascular
358 Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease
359 in outpatients with COVID-19. *J Med Vasc* 2020; **45**: 210–3.
- 360 13 Leonard-Lorant I, Delabranche X, Severac F, *et al.* Acute Pulmonary Embolism in
361 COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. *Radiology*
362 2020; : 201561; Apr 23, 2020 (Epub ahead of print).
- 363 14 Poissy J, Goutay J, Caplan M, *et al.* Pulmonary Embolism in COVID-19 Patients:
364 Awareness of an Increased Prevalence. *Circulation* 2020; : Apr 24, 2020 (Epub ahead of
365 print).

- 366 15 Klok FA, Kruij MJHA, van der Meer NJM, *et al.* Confirmation of the high cumulative
367 incidence of thrombotic complications in critically ill ICU patients with COVID-19: An
368 updated analysis. *Thromb Res* 2020; : Apr 30, 2020 (Epub ahead of print).
- 369 16 Helms J, Tacquard C, Severac F, *et al.* High risk of thrombosis in patients with severe
370 SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*
371 2020; : 1–10; May 4, 2020 (Epub ahead of print).
- 372 17 Middeldorp S, Coppens M, van Haaps TF, *et al.* Incidence of venous thromboembolism
373 in hospitalized patients with COVID-19. *J Thromb Haemost JTH* 2020; : May 05, 2020
374 (Epub ahead of print).
- 375 18 Lodigiani C, Iapichino G, Carenzo L, *et al.* Venous and arterial thromboembolic
376 complications in COVID-19 patients admitted to an academic hospital in Milan, Italy.
377 *Thromb Res* 2020; **191**: 9–14.
- 378 19 Llitjos J-F, Leclerc M, Chochois C, *et al.* High incidence of venous thromboembolic
379 events in anticoagulated severe COVID-19 patients. *J Thromb Haemost JTH* 2020; : Apr
380 22, 2020 (Epub ahead of print).
- 381 20 Fauvel C, Weizman O, Trimaille A, *et al.* Pulmonary embolism in COVID-19 patients: a
382 French multicentre cohort study. *Eur Heart J* 2020; published online July 13.
383 DOI:10.1093/eurheartj/ehaa500.
- 384 21 Revel M-P, Parkar AP, Prosch H, *et al.* COVID-19 patients and the radiology
385 department - advice from the European Society of Radiology (ESR) and the European
386 Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; published online April 20.
387 DOI:10.1007/s00330-020-06865-y.
- 388 22 Péré H, Podglajen I, Wack M, *et al.* Nasal Swab Sampling for SARS-CoV-2: a
389 Convenient Alternative in Times of Nasopharyngeal Swab Shortage. *J Clin Microbiol*
390 2020; **58**: May 26, 2020 (Epub ahead of print).
- 391 23 Gu XS, Rosenbaum PR. Comparison of Multivariate Matching Methods: Structures,
392 Distances, and Algorithms. *J Comput Graph Stat* 1993; **2**: 405–20.
- 393 24 PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian
394 and New Zealand Intensive Care Society Clinical Trials Group, Cook D, Meade M, *et al.*
395 Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011;
396 **364**: 1305–14.
- 397 25 Hull RD, Schellong SM, Tapson VF, *et al.* Extended-duration venous thromboembolism
398 prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized
399 trial. *Ann Intern Med* 2010; **153**: 8–18.
- 400 26 Goldhaber SZ, Leizorovicz A, Kakkar AK, *et al.* Apixaban versus Enoxaparin for
401 Thromboprophylaxis in Medically Ill Patients. *N Engl J Med* 2011; **365**: 2167–77.
- 402 27 Cohen AT, Spiro TE, Büller HR, *et al.* Rivaroxaban for Thromboprophylaxis in Acutely
403 Ill Medical Patients. *N Engl J Med* 2013; **368**: 513–23.

- 404 28 Cohen AT, Harrington RA, Goldhaber SZ, *et al.* Extended Thromboprophylaxis with
405 Betrixaban in Acutely Ill Medical Patients. *N Engl J Med* 2016; **375**: 534–44.
- 406 29 Petri M. Use of Hydroxychloroquine to Prevent Thrombosis in Systemic Lupus
407 Erythematosus and in Antiphospholipid Antibody–Positive Patients. *Curr Rheumatol*
408 *Rep* 2011; **13**: 77–80.
- 409 30 Poyiadji N, Cormier P, Patel PY, *et al.* Acute Pulmonary Embolism and COVID-19.
410 *Radiology* 2020; : 201955.
- 411 31 Wichmann D, Sperhake J-P, Lütgehetmann M, *et al.* Autopsy Findings and Venous
412 Thromboembolism in Patients With COVID-19. *Ann Intern Med* 2020; : May 06, 2020
413 (Epub ahead of print).
- 414 32 Smadja DM, Guerin CL, Chocron R, *et al.* Angiopoietin-2 as a marker of endothelial
415 activation is a good predictor factor for intensive care unit admission of COVID-19
416 patients. *Angiogenesis* 2020; published online May 27. DOI:10.1007/s10456-020-09730-
417 0.
- 418 33 Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary Vascular Endothelialitis,
419 Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; : May 21, 2020 (Epub
420 ahead of print).
- 421 34 Querol-Ribelles JM, Tenias JM, Grau E, *et al.* Plasma d-dimer levels correlate with
422 outcomes in patients with community-acquired pneumonia. *Chest* 2004; **126**: 1087–92.
- 423 35 Castro DJ, Pérez-Rodríguez E, Montaner L, Flores J, Nuevo GD. Diagnostic value of D
424 dimer in pulmonary embolism and pneumonia. *Respir Int Rev Thorac Dis* 2001; **68**:
425 371–5.
- 426 36 Spyropoulos AC, Levy JH, Ageno W, *et al.* Scientific and Standardization Committee
427 Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of
428 Venous Thromboembolism in Hospitalized Patients with COVID-19. *J Thromb Haemost*
429 *JTH* 2020; published online May 27. DOI:10.1111/jth.14929.
- 430 37 Cheng Y, Luo R, Wang K, *et al.* Kidney disease is associated with in-hospital death of
431 patients with COVID-19. *Kidney Int* 2020; **97**: 829–38.

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

Characteristic	PE patients (n = 59)	CTPA controls (n = 118)	CT controls (n = 118)	OR (95% CI) ^a	OR (95% CI) ^b
Age (years)	63 (53–79)	65 (54–78)	63 (53–78)	–	–
Male	33 (55.9)	68 (58.1)	66 (55.9)	–	–
BMI (kg/m ²)	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 ²	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)	–	–	–	–
Oxygen–support category^c					
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)
Treatment					

Hydroxychloroquine ^d	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 ^d	4 (6.9)	18 (15.5)	6 (5.4)	0.39 (0.12–1.20)	1.32 (0.31–5.57)
Outcome					
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. ^aPE patients versus CTPA controls; ^bPE patients versus CT controls; ^cHigher oxygen-support category during hospital stay. ^dbefore 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**

	PE patients (n = 59)	CTPA controls (n = 118)	CT controls (n = 118)	OR (95% CI)^a	OR (95% CI)^b
Radiologic characteristic					
Findings of COVID-19 on the first chest CT performed					
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)
Extent of lung damage on the first chest CT performed					
<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)
Location of PE					
Pulmonary trunk	12 (20.0)	–	–	–	–
Lobar artery	15 (25.5)	–	–	–	–
Segmental artery	24 (41.0)	–	–	–	–
Sub-segmental artery	8 (13.5)	–	–	–	–
Biological characteristic					
D-dimers ^c (ng/mL)	2605 (1436–7333)	1237 (885–2075)	–	5.11 (1.90–13.76)	–
Fibrinogen ^d (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 ^d (mg/L)	136 (56–244)	100 (30–158)	88 (25–131)	1.66 (0.84–3.27)	3.36 (1.58–7.14)
Hemoglobin ^e (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 ^e (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 ^e (M/L)	895 (697–1342)	860 (597–1242)	865 (662–1220)	1.55 (0.80–2.99)	1.46 (0.67–3.16)
Creatinine ^e (μmol/L)	75 (60–90)	77 (61–99)	76 (61–94)	0.77 (0.40–1.48)	0.86 (0.42–1.75)
ASAT ^e (IU/L)	49 (33–79)	48 (33–71)	40 (28–57)	1.15 (0.58–2.28)	1.71 (0.86–3.41)
ALAT ^e (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. ^aPE patients versus CTPA controls; ^bPE patients versus CT controls; ^cbefore CTPA assessment. ^dhigher level during hospitalisation.
443 ^elevel 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.**

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

447 ^aTwo 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%); ^bOptimal D-dimer
 449 according to the ROC curve. PE = pulmonary embolism; Se = sensitivity; Sp = specificity;
 450 NPV = negative predictive value; PPV = positive predictive value.