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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 Penalozza, Barbara Hernandez, Sebastien Beaune, Judith Gorlicki, Prabakar Vaittinada Ayar, et al.

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

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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.¹ COVID-19 viral pneumonia is associated
176 with hypoxia, a hyper-inflammatory state and coagulopathy.^{2,3} High rates of elevated
177 D-dimers have also been reported in case series, which may be associated with
178 worse outcomes.^{4,5} 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.⁶

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.⁷ 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.⁸⁻¹⁰ 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 1st
218 to April 10th 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 4th, 6th, 15th, 15th, 18th and 24th
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.¹¹

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%).^{12,13}

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).¹⁴

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.^{15,16}

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.^{17,18} 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.¹⁹

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 10th, 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.^{20,21} 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.^{22,23} 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.²⁰ 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.

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

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

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

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

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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

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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
Age (years), mean (SD)			
Sex			
Female	3253	234 (45%)	1471 (53%)
ED from France	3253	358 (72%)	2276 (83%)
Post pandemic period	3253	252 (50%)	1642 (51%)
Comorbidities			
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%)
ED presentation			
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)
Risk factors for PE			
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%)
Laboratory results			
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

		PE n=500	No PE n=2753
Signs of COVID-19			
Very likely		82 (16%)	470 (17%)
Compatible		54 (11%)	296 (11%)
Unlikely		364 (73%)	1987 (72%)
Extent of lesions			
	n=127		n=711
Moderate		35 (28%)	197 (28%)
Extended		47 (37%)	238 (33%)
Severe		40 (31%)	255 (36%)
Critical		5 (4%)	21 (3%)
RT-PCR COVID-19			
Performed		202 (40%)	1136 (41%)
Positive		80 (16%)	524 (19%)
Confirmed COVID-19		148 (30%)	826 (30%)

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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
Covid-19	0.95 [0.77 – 1.18]	0.66	0.98 [0.76 – 1.26]	0.86
Sexe male	1.34 [1.10 – 1.62]	0.0035	1.46 [1.18 – 1.80]	0.0005
Age (quartile)		0.0033		0.0186
[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	
Heart rate (bpm)	1.01 [1.00 – 1.01]	0.0007	1.01 [1.01 – 1.02]	<0.0001
Past thrombo-embolic event	2.41 [1.87 – 3.10]	<0.0001	2.32 [1.77 – 3.04]	<0.0001
Hemoptysis	0.81 [0.47 – 1.41]	0.46	0.84 [0.48 – 1.50]	0.56
Clinical sign of DVT	2.53 [1.95 – 3.28]	<0.0001	2.31 [1.73 – 3.08]	<0.0001
Recent immobilisation	1.93 [1.39 – 2.68]	<0.0001	1.92 [1.34 – 2.75]	0.0004
Active cancer	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