Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 197 (2021) 94–99

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

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

Benjamin Planquette[a,b,c,d,e,*], Alice Le Berre[f,g], Lina Khider[a,c,e,h,i], Alexandra Yannoutsos[g,i,j], Nicolas Gendron[a,b,c,e,k], Marie de Torcy[d,g], Nassim Mohamedi[e,i], Stéphane Jouveshomme[d,g], David M. Smadja[a,b,c,e,k,l], Isabelle Lazareth[g,i], Guillaume Goudot[a,c,e,h,i], Laure Fournier[a,e,f,m], Cédric Bruel[g,n], Jean Luc Diehl[a,b,c,e,n], Jean-Jacques Mourad[a,g,o], Guy Meyer[a,d,e,l,m,p], Pascal Priollet[g,i], Emmanuel Messas[a,e,h,i,m], Olivier Sanchez[a,b,c,d,e,l], Hélène Beaussier[g,q], Tristan Mirault[a,e,i,m], Marc Zins[f,g], Gilles Chatelier[a,e,p,r], Joseph Emmerich[a,g,i,j]

[a] Université de Paris, France
[b] Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France
[c] Biosurgical research lab (Carpentier Foundation), F-75015 Paris, France
[d] Department of Respiratory Medicine, France
[e] Assistance publique hôpitaux de Paris AH-HP, Hôpital européen Georges-Pompidou, F-75015 Paris, France
[f] Department of Radiology, France
[g] Groupe Hospitalier Paris Saint-Joseph, F-75014 Paris, France
[h] Physics for Medicine Paris, INSERM U1273, ESPCI Paris, CNRS FRE 2031, F-75011 Paris, France
[i] Department of Vascular Medicine, France
[j] INSERM CRESS UMR 1153, F-75005 Paris, France
[k] Department of Haematology, France
[l] F-CRIN INNOVTE, Saint-Étienne, France
[m] Paris research cardiovascular center PARCC INSERM UMR-S 970, F-75015 Paris, France
[n] Intensive Care Unit, France
[o] Department of Internal Medicine, France
[p] INSERM CIC 14-18, F-75015 Paris, France
[q] Department of Clinical Investigation, France
[r] Department of statistics, bioinformatics and public health, France

ARTICLE INFO

Keywords:
Pulmonary embolism
COVID-19
CTPA
D-dimer

ABSTRACT

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

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

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

* Corresponding author at: Department of respiratory medicine - Assistance Publique Hôpitaux de Paris, AH-HP, Hôpital européen Georges-Pompidou, 20 rue Leblanc, 75015 Paris, France.
E-mail address: benjamin.planquette@aphp.fr (B. Planquette).

https://doi.org/10.1016/j.thromres.2020.11.001
Received 1 August 2020; Received in revised form 12 October 2020; Accepted 3 November 2020
Available online 7 November 2020

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

1. Introduction

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

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

In the present analysis, we aimed to 1) evaluate the prevalence of PE among a large population of all consecutive patients admitted for COVID-19 pneumonia in two centers and 2) identify the characteristics associated with PE in those patients by using a nested case-control design with patients who underwent either unenhanced computed tomography (CT) or computed tomography pulmonary angiogram (CTPA).

2. Methods

2.1. Patients and study design

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

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

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

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

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

2.2. Clinical and laboratory data

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

Biological parameters at admission including complete blood count, aspartate and alanine aminotransferase (ASAT, ALAT), plasma creatinine were recorded. We report D-dimer values in PE patients and CTPA controls, using the STA®-Liatest® D-Di (Diagnostica Stago, Asnières, France) (GHPSJ) or the Vidas D-Dimer® assay (Biomérieux, Marcy-Etoile, France) (HEGP). During follow-up, highest values of C-reactive protein (CRP) and fibrinogen were also noted. Nasopharyngeal swabs were collected in universal transport medium (Xpert® nasopharyngeal sample collection kit) at hospital admission. SARS CoV-2 was detected using Allplex™ 2019-nCoV Assay (Seegene), a multiplex Real-time PCR assay that detects three target genes (E gene, RdRP gene and N gene) in a single tube, as previously described [22]. Only qualitative data were available.

2.3. Study outcomes

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

2.4. Statistical analysis

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

Categorical variables are presented as number of patients (percentages) and quantitative variables as median (interquartile range [IQR]). All percentages were calculated for available data for each variable. Unadjusted conditional logistic regression analysis, which accounted for the matched study design, was performed to evaluate the association of various clinical or biological characteristics with the risk of having PE. Odds ratios (OR) are displayed with their 95% confidence intervals (CI). To evaluate the diagnostic performance of D-dimer in predicting PE, receiver operating characteristic (ROC) curve analysis of D-dimer concentration prior to CTPA evaluation was performed. Youden's index (calculated as sensitivity + specificity − 1) was chosen to obtain the optimal D-dimer threshold. Sensitivity and specificity are calculated with standard formulas. The positive and negative predictive values (PPV and NPV) were calculated with the Bayes' theorem with the PE prevalence obtained in the whole cohort (5.6%) and in the cohort with CTPA (21.2%). Statistical analyses were performed using the NCSS 2020 statistical software.

3. Results

3.1. Population

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

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

3.2. Clinical characteristics

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

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)

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

associated with a decreased risk of PE.

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

3.3. Radiological and biological characteristics

The main radiological and biological characteristics of the cases and controls are summarized in Table 2. There was no difference between PE patients and the two control groups in terms of CT findings suggestibility for COVID-19 on the first CT scan, with highly suggestive features found in a majority of patients in all groups. PE patients exhibited more extensive lesions than the CT controls (OR 3.9; 95% CI 1.54–9.94, for a parenchymal involvement >50%). At admission, there was no difference among PE patients and the two control groups regarding hemoglobin level, platelet count, lymphocyte count, creatinine, ASAT and ALAT levels. Regarding inflammation during the hospitalization, assessed by both CRP and fibrinogen, PE diagnosis tends to be associated with increased levels of these biomarkers. The risk of PE was significantly associated with CRP elevation (OR 3.36; 95% CI 1.58–7.14) compared to CT controls.

3.4. D-dimer level

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

4. Discussion

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

Furthermore, compared to recent prevention studies in acutely ill medical patients, the prevalence of PE in our population is 10 times higher than the prevalence observed in these randomized trials, demonstrating the high thrombotic risk associated with COVID-19 [25–28]. Nevertheless, it remains difficult to draw definite conclusions by comparing incidence measured in randomized studies in ICU to

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)

Continuous parameters are reported as median (IQR) and data expressed as *n* (%). All percentages were calculated for available data for each variable.

[a] PE patients versus CTPA controls.

[b] PE patients versus CT controls.

[c] Before CTPA assessment.

[d] Higher level during hospitalization.

[e] level at admission PE = pulmonary embolism; CTPA = computed tomography pulmonary angiogram; CT = unenhanced computed tomography; OR = odds ratio.

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

	PE					PE prevalence in COVID-19 patients[a]			
						5.6%		21.2%	
	Confirmed	Excluded	Total	Se	Sp	NPV	PPV	NPV	PPV
D-dimer ≥ 500 ng/mL									
≥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]									
≥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									
≥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									
≥3500	20	10	30	43.5	90.0	96.4	20.3	85.6	53.3
<3500	26	90	116						
Total	46	100	146						

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

prevalence observed in our retrospective series. In COVID-19 patients who had CTPA performed, we found a PE prevalence of 21.2%. Recently, 4 studies of less than 200 COVID-19 patients, mainly hospitalized in ICU, found a similar prevalence of PE between 13.5% and 30% [14–17]. Interestingly, almost half of the PE episodes were diagnosed at hospital admission as previously described [18], suggesting that PE should be suspected at COVID-19 diagnosis in patients with respiratory symptoms. Furthermore, for hospitalized patients PE occurred despite the fact that patients received prophylactic anticoagulation, either with regular or higher doses, as physicians were aware of the higher thrombotic risk in this population. The protective effect of hydroxychloroquine on thrombotic events in systemic lupus erythematosus was not observed in our COVID-19 population [29].

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

Interestingly and in accordance with another report [30], the mortality did not differs between groups suggesting that PE does not impact patient's survival in this COVID-19 population.

Patients with PE tended to have a higher CRP than patients in the 2 control groups and to present more extensive COVID-19 lung damages. Those findings have been related to a more severe COVID-19 associated coagulopathy [10]. Two other French studies showed that PE was more frequent in ICU COVID-19 patients when compared to ARDS non-COVID-19 patients [16] or patients with influenza infection [14]. Finally, our data are concordant with the hypothesis of a specific effect of the SARS-CoV-2 infection in thrombosis and inflammation. A recent autopsy study demonstrated a high incidence of thromboembolic events associated with COVID-19 coagulopathy (58%), but histology also demonstrated microvascular thrombosis [31]. Clinical and pathology studies demonstrated endothelial injury [32] associated with intracellular SARS-CoV-2 infection, widespread microangiopathy of alveolar capillaries and angiogenesis, features that appeared different from influenza A (H1N1) infection [33]. Furthermore, recently, our team showed that therapeutic anticoagulation at admission could prevent COVID-19-associated endothelial injury [6].

Previous reports [1,4–8] have shown that D-dimer levels are increased during COVID-19-associated coagulopathy and higher D-dimer levels at admission are associated with VTE during follow-up [17]. The use of high D-dimer thresholds, such as 3500 ng/mL, is not effective enough to diagnose PE or initiate therapeutic anticoagulation, as we showed that the D-dimer positive predictive value in patients with suspected PE was only 50%. As previously published D-dimer are increased in pneumonia and associated with radiologic pneumonia extension [34] Furthermore, in patients diagnosed with community-acquired pneumonia, D-dimers where more elevated in patients with high probability PE [35].

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

Our study has a few limitations. First this is a retrospective series due to the emergency of the health crisis. Second outcomes analysis may be biased because some patients were still hospitalized at the time of data collection and other patients were transferred to other hospitals. Thus, it may lead to immortal time bias, potentially affecting the PE prevalence. Finally, screening for PE is mainly dependent on the decision to perform CTPA i.e. for clinical suspicion of PE and in patients with worsening of oxygen dependence or acute degradation of hemodynamic status. But, as the practice of CTPA investigations was not pre-defined according to specific criteria but left to the appreciations of the different clinicians in charge of the patients; obviously more severe patients received CTPA. To circumvent this potential limitation, we performed a nested case-control study in our large population of 1042 patients with COVID-19 acute respiratory syndrome. On the contrary, the fact that only one quarter of the studied population had a CTPA probably underestimates the rate of PE.

5. Conclusion

Our study results suggest a PE prevalence in COVID-19 patients close to 5% in the whole population and to 20% of the clinically suspected population. D-dimer could be an interesting tool in the diagnostic

strategy of PE as long as the threshold is adjusted to the COVID-19 associated coagulopathy. Further prospective studies are necessary to confirm the thresholds of D-dimer analyzed here, and to alert physicians on the high risk of PE in this setting.

Acknowledgements

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

References

[1] W. Guan, Z. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720.
[2] Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA* 2020; published online April 24. DOI:https://doi.org/10.1001/jama.2020.6825.
[3] J.-L. Diehl, N. Peron, R. Chocron, et al., Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study, Ann. Intensive Care 10 (2020) 95.
[4] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062.
[5] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemost. 18 (2020) 844–847.
[6] Khider L, Gendron N, Goudot G, *et al.* Curative anticoagulation prevents endothelial lesion in COVID-19 patients. *J Thromb Haemost JTH* 2020; published online June 18. DOI:https://doi.org/10.1111/jth.14968.
[7] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (2020) 1061.
[8] T. Chen, D. Wu, H. Chen, et al., Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study, BMJ 368 (2020) m1091.
[9] H. Han, L. Yang, R. Liu, et al., Prominent changes in blood coagulation of patients with SARS-CoV-2 infection, Clin. Chem. Lab. Med. 58 (2020) 1116–1120.
[10] J. Thachil, N. Tang, S. Gando, et al., ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J. Thromb. Haemost. 18 (2020) 1023–1026.
[11] B. Bikdeli, M.V. Madhavan, D. Jimenez, et al., COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review, J. Am. Coll. Cardiol. 75 (2020) 2950–2973.
[12] L. Khider, S. Soudet, D. Laneelle, et al., Proposal of the French Society of Vascular Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease in outpatients with COVID-19, J Med Vasc 45 (2020) 210–213.
[13] Leonard-Lorant I, Delabranche X, Severac F, *et al.* Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. *Radiology* 2020: 201561; Apr 23, 2020 (Epub ahead of print).
[14] Poissy J, Goutay J, Caplan M, *et al.* Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. *Circulation* 2020: Apr 24, 2020 (Epub ahead of print).
[15] Klok FA, Kruip MJHA, van der Meer NJM, *et al.* Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020; Apr 30, 2020 (Epub ahead of print).
[16] Helms J, Tacquard C, Severac F, *et al.* High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; 1–10; May 4, 2020 (Epub ahead of print).
[17] Middeldorp S, Coppens M, van Haaps TF, *et al.* Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost JTH* 2020; May 05, 2020 (Epub ahead of print).
[18] C. Lodigiani, G. Iapichino, L. Carenzo, et al., Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thromb. Res. 191 (2020) 9–14.
[19] Llitjos J-F, Leclerc M, Chochois C, *et al.* High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost JTH* 2020; Apr 22, 2020 (Epub ahead of print).
[20] Fauvel C, Weizman O, Trimaille A, *et al.* Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J* 2020; published online July 13. DOI:https://doi.org/10.1093/eurheartj/ehaa500.
[21] Revel M-P, Parkar AP, Prosch H, *et al.* COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; published online April 20. DOI:https://doi.org/10.1007/s00330-020-06865-y.
[22] Péré H, Podglajen I, Wack M, *et al.* Nasal swab sampling for SARS-CoV-2: a Convenient alternative in times of nasopharyngeal swab shortage. *J Clin Microbiol* 2020; **58**: May 26, 2020 (Epub ahead of print).
[23] X.S. Gu, P.R. Rosenbaum, Comparison of multivariate matching methods: structures, distances, and algorithms, J. Comput. Graph. Stat. 2 (1993) 405–420.
[24] PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, D. Cook, M. Meade, et al., Dalteparin versus unfractionated heparin in critically ill patients, N. Engl. J. Med. 364 (2011) 1305–1314.
[25] R.D. Hull, S.M. Schellong, V.F. Tapson, et al., Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial, Ann. Intern. Med. 153 (2010) 8–18.
[26] S.Z. Goldhaber, A. Leizorovicz, A.K. Kakkar, et al., Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients, N. Engl. J. Med. 365 (2011) 2167–2177.
[27] A.T. Cohen, T.E. Spiro, H.R. Büller, et al., Rivaroxaban for thromboprophylaxis in acutely ill medical patients, N. Engl. J. Med. 368 (2013) 513–523.
[28] A.T. Cohen, R.A. Harrington, S.Z. Goldhaber, et al., Extended thromboprophylaxis with betrixaban in acutely ill medical patients, N. Engl. J. Med. 375 (2016) 534–544.
[29] M. Petri, Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody–positive patients, Curr. Rheumatol. Rep. 13 (2011) 77–80.
[30] Poyiadji N, Cormier P, Patel PY, *et al.* Acute pulmonary embolism and COVID-19. *Radiology* 2020; 201955.
[31] Wichmann D, Sperhake J-P, Lütgehetmann M, *et al.* Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Ann Intern Med* 2020; May 06, 2020 (Epub ahead of print).
[32] Smadja DM, Guerin CL, Chocron R, *et al.* Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. *Angiogenesis* 2020; published online May 27. DOI:https://doi.org/10.1007/s10456-020-09730-0.
[33] Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary vascular endothelialitis, Thrombosis, and angiogenesis in covid-19. *N Engl J Med* 2020; : May 21, 2020 (Epub ahead of print).
[34] J.M. Querol-Ribelles, J.M. Tenias, E. Grau, et al., Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia, Chest 126 (2004) 1087–1092.
[35] D.J. Castro, E. Pérez-Rodríguez, L. Montaner, J. Flores, G.D. Nuevo, Diagnostic value of D dimer in pulmonary embolism and pneumonia, Respir Int Rev Thorac Dis 68 (2001) 371–375.
[36] Spyropoulos AC, Levy JH, Ageno W, *et al.* Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost JTH* 2020; published online May 27. DOI:https://doi.org/10.1111/jth.14929.
[37] Y. Cheng, R. Luo, K. Wang, et al., Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (2020) 829–838.