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" Impact clinique de la survenue d'une embolie pulmonaire chez les patients ventilés mécaniquement en raison d'un syndrome de détresse respiratoire aigu lié au COVID-19 "

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Table des matières

Introduction

La pandémie de COVID-19 a été associée à la survenue d'un très grand nombre d'hospitalisations en milieu de soins intensifs et cela en raison d'insuffisances respiratoires hypoxémiques sévères nécessitant un soutien respiratoire avancé. Sur la période pandémique de mars 2020 à mai 2022, un total de 482 patients ont été pris en charge aux soins intensifs adultes des Hôpitaux Universitaires de Genève pour une insuffisance respiratoire hypoxémique due au COVID-19. Tous ces patients présentaient la constellation clinique du syndrome de détresse respiratoire aigu (ARDS) [1] et 76.8% d'entre eux ont nécessité une intubation associée à une ventilation mécanique par pression positive (données non publiées issues de la base de données du service des soins intensifs adultes des Hôpitaux Universitaires de Genève).

Selon les données d'études interventionnelles récentes, l'embolie pulmonaire (EP) est une complication touchant moins de 2 à 3% des patients durant leur séjour aux soins intensifs [2-4]. La prévalence de l'EP dans la sous-population des patients présentant un ARDS non secondaire au COVID-19 est quant à elle très peu étudiée et serait d'un ordre similaire de 1.5 à 3% [5, 6]. Néanmoins, chez les patients COVID-19, une très grande variabilité de prévalence de l'embolie pulmonaire a été retrouvée dans la littérature, essentiellement en raison de dissemblances lors de la sélection des patients et de la non-uniformité des procédures employées pour dépister les événements thromboemboliques [7-9]. Il a été cependant démontré que la prévalence de l'EP s'accroit avec l'augmentation de la sévérité de la maladie [10], avec chez les patients présentant un ARDS secondaire au COVID-19 (CARDS), l'EP pouvant être jusqu'à 10 fois plus fréquente que dans une population d'ARDS non liés au COVID-19 [5, 6].

La physiopathologie de la coagulopathie liée au COVID-19 est complexe et n'est pour l'heure pas entièrement comprise [11, 12]. Une dysfonction de l'endothélium vasculaire semble être un contributeur majeur à sa pathogenèse [13, 14]. L'infection par le SARS-CoV-2 engendre en effet une dérégulation des systèmes anti-coagulants se trouvant au sein du glycocalyx tapissant l'endothélium et favorise donc l'expression de facteurs procoagulants tels que le facteur tissulaire. Lors de l'infection des voies respiratoires par le SARS-CoV-2, ce phénomène se produit essentiellement au niveau des membranes alvéolo-capillaires, menant à des dommages de l'endothélium vasculaire et favorisant des phénomènes de thrombose microvasculaire [15, 16]. Parallèlement, l'infection par le SARS-Cov-2 mène à une décharge inflammatoire majeure, parfois appelée « tempête cytokinique » [17], stimulant le système immunitaire inné et pouvant également contribuer indirectement aux lésions pulmonaires du COVID-19 [18]. Dans les cas d'atteintes sévères liées au SARS-CoV-2, un phénomène similaire se produit au sein de l'endothélium vasculaire systémique, pouvant précipiter la survenue de thromboses veineuses profondes et par conséquent d'embolies pulmonaires. D'autres voies d'activation de la coagulation sont encore concernées dans la physiopathologie complexe de la coagulation liée au COVID-19, telles que la dérégulation du système kallikrein-kinnin [19], une hyperactivation du complément [20, 21], ou une dysfonction plaquettaire [22].

L'impact clinique de la survenue d'une EP chez des patients hospitalisés pour une atteinte respiratoire du COVID-19 dans des unités de soins aigus ou de soins intermédiaires a été largement étudié. Il a en effet été démontré que les patients présentant une EP durant leur séjour étaient plus souvent admis aux soins intensifs, nécessitaient plus souvent un soutient ventilatoire invasif et avaient des durées de séjour et une mortalité plus élevées [23-26]. L'association entre la survenue d'une EP et une augmentation de la mortalité dans une

population de patients de soins intensifs reste cependant plus floue, d'autant plus chez les patients sous ventilation mécanique invasive [9, 24, 27]. Par ailleurs, très peu de données sont disponibles concernant l'impact de l'embolie pulmonaire sur d'autres aspects cliniques, tels que la durée de ventilation mécanique, la nécessité d'oxygénation par membrane extracorporelle (ECMO) ou les durées de séjours en milieu de soins intensifs et hospitalière. Finalement, aucune étude ne s'est jusqu'alors, spécifiquement, consacrée à l'impact de la survenue d'une embolie pulmonaire au sein de la sous-population des patients sous ventilation mécanique invasive en lien avec un CARDS.

Sur la base de ces constatations, le but de la présente thèse et de l'étude rétrospective associée a été d'explorer l'impact pronostic que peut avoir la survenue d'une EP (diagnostiquée sur des critères cliniques) chez des patients adultes sous ventilation mécanique invasive pour un CARDS au sein du service des soins intensifs des Hôpitaux Universitaires de Genève. Secondairement, et principalement dans le but de réduire un biais diagnostique de l'embolie pulmonaire au sein de notre cohorte, nous avons cherché à décrire son impact pronostic au sein de la sous-populations des patients ayant eu un dépistage idéal et méthodique de l'EP durant leur séjour. Finalement, nous nous sommes intéressés à l'impact que pouvait avoir une EP sur le devenir des patients les plus graves assistés par à la fois une assistance ventilatoire mécanique et une ECMO.

Article de publication originale

Pulmonary embolism impacts clinical outcomes of intubated patients with acute respiratory distress syndrome related to COVID-19

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Original Article

Pulmonary embolism impacts clinical outcomes of intubated patients with acute respiratory distress syndrome related to COVID-19

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ABSTRACT

Background: Pulmonary embolism (PE) in critically ill patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 is a major complication which might impact survival. We aimed to determine the prevalence of PE and assess its impact of PE on clinical outcomes in intubated patients with ARDS due to COVID-19.
Methods: All intubated patients with ARDS due to COVID-19 admitted to the intensive care unit (ICU) of Geneva University Hospitals between March 9, 2020, and May 31, 2022, were included. A retrospective analysis was conducted on the occurrence of PE and its association with clinical outcomes. The primary outcome was ventilator-free days during the first 28 days after ICU admission. Linear regressions were performed to investigate the association between PE and outcomes.
Results: Among the 370 intubated patients with ARDS related to COVID-19, 58 (15.7%) presented with PE. Patients with PE had significantly fewer ventilator-free days than patients without PE (median (IQR) of 3 (0−11) days *versus* 12 (0−19) days; $p < 0.001$). Mortality did not differ significantly between groups (12/58 [20.7%] of patients with PE *versus* 71/312 [22.8%] of patients without PE; $p = 0.72$). Duration of IMV, and ICU and hospital LOS were significantly longer among patients with PE. The need for ECMO support was similar among both groups.
Conclusions: The occurrence of PE in patients with ARDS due to COVID-19 had a significant impact on clinical outcomes. They had fewer ventilator-free days, longer duration of IMV, and longer ICU and hospital lengths of stay. However, pulmonary embolism was not associated with higher mortality.
Ethics approval: Ethical committee of Geneva (BASEC #: 2020-00917).

1. Introduction

Coronavirus disease 2019 (COVID-19) is associated with a prothrombotic state and high risk of venous thromboembolic events [1]. The complex pathophysiology of COVID-19-related coagulopathy involves various pathways including cytokine storm, platelet activation, endothelial cell activation, and coagulation pathways activation [2]. Micro- and macrovascular thrombotic events have been proposed as possible mechanisms for severe hypoxemia associated with COVID-19 [3].

Pulmonary embolism (PE) may be up to 10 times more common among patients with COVID-19-related acute respiratory distress syndrome (ARDS) compared to those with ARDS from other causes [4]. Also, the prevalence of PE among COVID-19 patients admitted to the intensive care unit (ICU) appears higher than in those not requiring ICU [5–8]. However, the exact prevalence of PE in COVID-19 patients remains unclear, with differing estimates ranging from 6% to 43% [6,9,10]. The variance may be attributed to differences in cohort size, screening strategies, timing of publication, and patient selection. High-quality data are lacking regarding the occurrence of PE among intubated COVID-19 patients with ARDS.

Pulmonary embolism occurrence has been linked to higher rates of ICU admission, a higher need for mechanical ventilation, a longer length of stay (LOS), and a higher mortality in COVID-19 patients hospitalized in intermediate care or onward [8,11–13]. The impact of PE on clinical outcomes has however not been studied among intubated patients with ARDS due to COVID-19. An association between PE and mortality in critically ill COVID-19 patients remains unclear [6,11,14]. In addition, little information

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exists on the impact of PE on important outcomes such as the duration of mechanical ventilation, the need for extracorporeal membrane oxygenation, and ICU and hospital lengths of stay.

Given this knowledge gap, our aim was to investigate the prevalence of PE in a large cohort of intubated COVID-19 patients with ARDS and to gain insight into the prognostic impact of PE occurrence on important patient-centred outcomes.

2. Patients and methods

2.1. Study design and patients

This single-center retrospective observational study was conducted in the ICU of Geneva University Hospitals (Geneva, Switzerland), between March 9, 2020, and May 31, 2022. All adult patients admitted to the ICU requiring invasive mechanical ventilation for acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 infection were included. COVID-19 diagnosis was confirmed through laboratory confirmation of SARS-CoV-2 infection using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on a nasopharyngeal swab and/or in bronchoalveolar lavage (BAL) fluid. Patients were classified according to the fact that they were diagnosed with pulmonary embolism during their hospital stay or not.

The institutional ethics committee approved the present study (Swiss BASEC Number: 2020-00917) and informed consent was obtained from either the patient or the next-of-kin.

2.2. Data collection

All demographic characteristics, severity scores and biological data were collected at the time of ICU admission. The Charlson Comorbidity Index was used to estimate the burden of comorbidities [15]. Therapies such as medications, mechanical ventilation, prone positioning, renal replacement therapy, and extracorporeal membrane oxygenation (ECMO), as well as complications such as ventilatory associated pneumonia (VAP) and thrombotic events were recorded during ICU stay. ARDS was defined according to Berlin's definition [16].

The presence of pulmonary embolism was defined as the presence of thrombus in pulmonary arteria confirmed either by computed tomography pulmonary angiogram (CTPA), pulmonary scintigraphy, or by direct visualization with transesophageal echocardiography. Research of PE was based on the suspicion of the clinician in charge. No systematic CTPA were performed during the study period. The severity of pulmonary embolism was classified according to the European Society of Cardiology (ESC) classification [17]. We also evaluated the repartition of pulmonary thrombi and the timing of PE diagnosis. Deep vein thrombosis (DVT) was diagnosed by ultrasound exploration done by angiologists. A patient with a diagnosis of PE was systematically screened for DVT in our institution. Among patients without PE, ultrasound exploration for DVT was only done if clinically suspected by the clinician in charge. Thromboprophylaxis was administered upon hospital admission according to institutional guidelines. Briefly, an intermediate dose prophylaxis was recommended early after the beginning of the pandemic up to July 2021, and a standard prophylaxis was used after that period. The choice of the anticoagulant agent, either unfractionated heparin or low-molecular-weight heparin, was left to the clinician's discretion, and doses were adapted to BMI. Intermittent pneumatic compressions of the lower limbs were used for patients with contraindications to a pharmacologic thromboprophylaxis. Patients were followed until hospital discharge or death.

2.3. Outcomes

The primary outcome was ventilator-free days during the first 28 days of ICU admission, defined as the number of days alive and free from invasive mechanical ventilation for at least 48 consecutive hours [18]. If the patient was re-intubated within 48 h of the extubation the variable was treated as zero ventilator-free days; if re-intubated after 48 h, the 48 h period was counted as ventilator-free days. Patients discharged from the ICU before 28 days were considered alive and free from invasive mechanical ventilation at 28 days. Nonsurvivors at day 28 were considered to have zero ventilator-free days. We chose the criterion of ventilator-free days because it associates mortality and mechanical ventilation duration in surviving patients.

The secondary outcomes include the PE prevalence and classification according to ESC classification, the duration of invasive mechanical ventilation (IMV), Day-28 and hospital mortality, the use of adjunctive therapies for ARDS such as prone positioning, neuromuscular blockade, inhaled nitric oxide, and ECMO support, the occurrence of ventilatory associated pneumonia, and ICU and hospital lengths of stay.

2.4. Statistical analysis

Patients' characteristics were summarized with descriptive statistics. Counts and percentages were used for categorical variables. Mean (standard deviation [SD]) and median (interquartile range [IQR]) were used for the description of quantitative variables, as appropriate. Due to the low number of missing data, a complete case analysis was done. Statistical differences in categorical variables were determined using chi-squared or Fisher's exact test, as appropriate. Differences in continuous variables were determined using student t test, analysis of variance, or Mann-Whitney test, as appropriate. Univariable and multivariable linear regressions were conducted to characterize the association between PE and ventilator-free days. The following clinically relevant variables were determined a priori as potential confounding factors and were included in the multivariable analysis: SAPS II score and categorized BMI (BMI $>$ 30 kg/m^2) [19,20]. In order to take into account the burden of comorbidities in our model we also included the Charlson comorbitiy index as an independent variable. To investigate the association between PE and Day-28 mortality, we performed a multivariate logistic regression, adjusting the estimates for SAPS II, and categorized BMI and Charlson comorbidity index. The results of the linear regression are presented as regression coefficients with 95% confidence intervals (95% CI). The results of the logistic regression are expressed as odds ratios (OR) and 95% confidence intervals (95% CI).

Since no systematic screening for PE was performed during the study period and in order to mitigate a possible diagnostic bias, we performed a subgroup analysis among patients that had a screening for PE before ICU admission or during their ICU stay. We also assessed theses outcomes among patients needing ECMO support.

A two-tailed p value less than 0.05 was considered statistically significant. All statistical analyses were conducted using STATA, version 17 (StataCorp LLC, Texas, USA).

3. Results

In this study, 370 patients met the inclusion criteria and were included. A total of 58 patients presented with PE, an incidence of 15.7%. The median [IQR] age was 63 [56−72] years old, 273 (73.8%) patients were male, with a median BMI of 29.3 [25–32] kg/m^2. The

Table 1
Baseline characteristics of patients.

	All patients (*n* = 370)	No pulmonary embolism (*n* = 312)	Pulmonary embolism (*n* = 58)	*p*-value
Age, median (IQR)	63 (56–72)	63 (56–72)	64 (58–73)	0.72
Male, *n* (%)	273 (73.8)	223 (71.5)	50 (86.2)	0.01
BMI, median (IQR)	29.3 (25–32)	29.4 (25–32)	28.9 (25–34)	0.50
SOFA, median (IQR)	5 (4–7)	5 (4–7)	5 (3–6)	0.08
SAPS II, median (IQR)	56 (43–69)	55 (43–69)	56 (43–66)	0.76
Time in days from hospital to ICU admission, median (IQR)	2 (1–4)	2 (1–4)	2 (0–5)	0.69
Admission from, *n* (%)				0.32
Prehospital care	11 (3)	10 (3.2)	1 (1.7)	
Emergency department	54 (14.6)	41 (13.1)	13 (22.4)	
Medical ward	44 (11.9)	40 (12.8)	4 (6.9)	
Intermediate care unit	219 (59.2)	185 (59.3)	34 (58.6)	
Other hospital	41 (11.1)	35 (11.2)	6 (10.3)	
Charlson Comorbidity Index, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.09
Comorbidities, *n* (%)				
Hypertension	171 (46.2)	150 (48.1)	21 (36.2)	0.09
Diabetes	117 (31.6)	107 (34.3)	10 (17.2)	0.01
COPD	24 (6.5)	23 (7.4)	1 (1.7)	0.10
Cardiovascular disease	73 (19.7)	64 (20.5)	9 (15.5)	0.38
Cerebrovascular disease	26 (7)	23 (7.4)	3 (5.2)	0.54
Malignancy[a]	35 (9.5)	32 (10.3)	3 (5.2)	0.22
Chronic kidney disease	31 (8.4)	29 (9.3)	2 (3.4)	0.14
No comorbidity	78 (21.1)	58 (18.6)	22 (37.9)	0.001
Laboratory values, median (IQR)				
C-reactive protein, mg/L	120 (55–188.5)	130 (62.3–191.6)	70 (17.7–179.9)	0.15
Leucocyte, $\times 10^9$/L	8.9 (6.4–12.4)	9 (6.3–12.4)	8.8 (7.1–12.1)	0.95
Thrombocyte, $\times 10^9$/L	224 (178–295)	218 (174–288)	262 (210–314)	0.08
D-dimer, µg/L	1476 (882–2609)	1349 (859–2255)	2430 (1209–9999)	<0.001
Creatinine, µmol/L	0.88 (0.71–1.19)	0.89 (0.71–1.21)	0.86 (0.71–1.17)	0.42
Bilirubin, mg/dL	0.53 (0.35–0.77)	0.47 (0.35–0.71)	0.59 (0.37–0.82)	0.26
h sTroponin T, ng/L	17 (10–38.5)	16.5 (10–38.8)	23 (10.5–38)	0.49
Arterial lactate, mmol/L	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.3 (1.1–1.7)	0.13
PaO_2/FiO_2 ratio, mmHg	106 (82.5–143.3)	108 (82.5–144.8)	104 (81–132)	0.24
Severity of ARDS, n (%)				0.46
Mild	27 (7.3)	25 (8)	2 (3.4)	
Moderate	182 (49.2)	152 (48.7)	30 (51.7)	
Severe	159 (43)	133 (42.6)	26 (44.8)	
Treatments for COVID-19, n (%)				
Remdesivir	31 (8.3)	26 (8.33)	5 (8.6)	0.94
Corticosteroids for COVID-19	234 (63.2)	183 (58.6)	51 (87.9)	<0.001
Corticosteroids for other indications[b]	140 (37.8)	112 (35.9)	28 (48.2)	0.07
Tocilizumab	92 (24.9)	59 (18.9)	33 (56.9)	<0.001
Anticoagulation regimen at ICU admission, n (%)				<0.001
Standard dose prophylaxis	173 (46.8)	147 (47.1)	26 (44.8)	
Intermediate dose prophylaxis	147 (39.7)	134 (42.9)	13 (22.4)	
Therapeutic anticoagulation	44 (11.9)	26 (8.3)	18 (31)	
No anticoagulation	6 (1.6)	5 (1.6)	1 (1.7)	
Deep vein thrombosis, *n* (%)	31 (8.4)	17 (5.4)	14 (24.1)	0.001

ARDS acute respiratory distress syndrome, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *SOFA* sequential organ failure assessment, *SAPS II* simplified acute physiology score II, *APACHE II* acute physiology and chronic health evaluation II, PaO_2 arterial partial pressure of oxygen, FiO_2 inspired fraction of oxygen.
[a] Malignancy includes solid or hematologic neoplasia which are active or in remission.
[b] Other indications include septic shock, unresolving ARDS, asthma or COPD exacerbation, vasculitis, laryngeal edema or unspecified indication.

median SAPS II, and SOFA scores were 56 [43–69], and 5 [4–7], respectively, and did not differ significantly between groups. The main comorbidity was hypertension (171/370 patients, 46.2%), followed by diabetes (117/370 patients, 31.6%). The median Charlson Comorbidity Index was 3 [2–4] and was similar among groups. All patients in the PE group had a CTPA for diagnosis of the embolic event and 229/312 (73%) of the patients without PE had a screening for PE with a CTPA during their hospital stay. Patients were mainly transferred from intermediate care units (219/370, 59.2%), or from prehospital care and the emergency department (65/370, 17.6%) to the ICU after a median of 2 (1–4) days after hospital admission.

There were significantly more men (50/58 (86.6%) *versus* 223/312 (71.5%); $p = 0.01$) among patients presenting with PE compared to patients without PE. Patients with PE were less frequently diabetic (10/58 (17.2%) *versus* 107/312 (34.3%); $p = 0.01$) and had significantly higher D-dimers titles (median of 2430 [1209–9999] *versus* 1349 [859–2255] µg/L; $p < 0.001$). All other laboratory variables were similar among both groups. The severity of ARDS at admission was moderate to severe according to Berlin's classification and PaO_2/FiO_2 ratios at admission were similar between the two groups (median of 108 [82.5–144.8] mmHg for patients without PE and 104 [81–132] mmHg for patients with PE; $p = 0.24$). Patients with PE received also significantly more corticosteroids for COVID-19 (51/58 (87.9%) *versus* 183/312 (58.6%); $p < 0.001$) and tocilizumab (33/58 (56.9) *versus* 59/312 (18.9); $p < 0.001$) than patients without PE. All other baseline characteristics of patients were similar among both groups and can be found in Table 1.

The classification of severity according to ESC classification was the following among the 58 PE events: 6 (10.3%) were low risk, 27 (46.6%) were intermediate to low risk, 18 (31%) were intermediate

Table 2
Primary and secondary outcomes.

		All patients (n = 370)	No pulmonary embolism (n = 312)	Pulmonary embolism (n = 58)	p-value
Primary outcome	Days alive and ventilator-free at D-28, median (IQR)	10 (0–18)	12 (0–19)	3 (0–11)	<0.001
Secondary outcomes	Days under IMV, median (IQR)	13 (8–21)	12 (8–19)	18 (11–32.5)	<0.001
	Day-28 mortality, n (%)	83 (22.4)	71 (22.8)	12 (20.7)	0.72
	Hospital mortality, n (%)	106 (28.6)	87 (27.9)	19 (32.8)	0.46
	ICU length of stay, median (IQR)	16 (10–24)	15 (10–22)	22 (13–33.8)	<0.001
	Hospital length of stay, median (IQR)	28 (19–43)	27 (19–40)	39 (27–53.8)	0.03
	Adjunctive therapies for ARDS				
	Prone positioning, n (%)	292 (78.9)	245 (78.5)	47 (81.0)	0.66
	Number of prone sessions, median (IQR)	2 (1–3)	2 (1–3.8)	2 (1–3)	0.95
	Inhaled nitric oxyde, n (%)	100 (27)	73 (23.4)	27 (46.6)	<0.001
	ECMO, n (%)	36 (9.7)	27 (8.6)	9 (15.5)	0.10
	In-hospital complications, n (%)				
	Ventilatory associated pneumonia	89 (24.1)	68 (21.8)	21 (36.2)	0.01
	AKI requiring RRT	28 (7.6)	25 (8)	3 (5.2)	0.45

AKI acute kidney injury, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *RRT* renal replacement therapy.

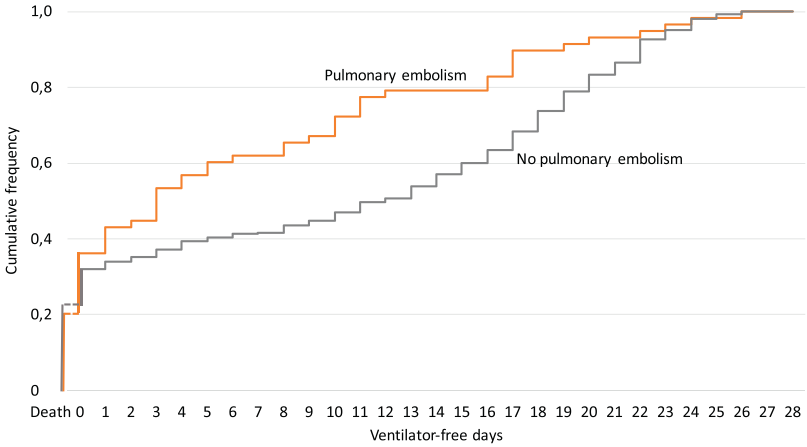

Fig. 1. Cumulative frequency of ventilator-free days according to study group.
The dashed lines represent patients who died (assigned to 0 ventilator-free days), and solid lines represent the cumulative frequency of patients who were receiving invasive mechanical ventilation all 28 days (assigned to 0 ventilator-free days) and then the cumulative frequency of patients who no longer required ventilation for an increasing number of days.

to high risk, 6 (10.3%) were high risk, and 1 (1.7%) could not be classified. Five patients (8.6%) received thrombolysis because of hemodynamic instability. The remaining high-risk PE was treated with ECMO support. The localization of PE was bilateral in 31 patients (53%), and 14 (24%) were truncular, 8 (14%) lobar, 28 (48%) segmental, and 8 (14%) subsegmental pulmonary embolisms. The median time between ICU admission and PE diagnosis was 3.5 (0–9) days. The diagnosis of PE was made before or within 72 h of ICU admission in 40 (69%) patients. The finding of deep vein thrombosis was significantly more frequent among patients presenting with a PE (14/58 (24.1%) *versus* 17/312 (5.4%); p = 0.001). Anticoagulation regimens at ICU admission differed statistically between the two groups, with therapeutic anticoagulation being more frequent among patients with PE. The main indication for therapeutic anticoagulation among patients with PE was confirmed acute PE or DVT (16/18, 88.9%), whereas it was stroke prevention in the context of supraventricular arrythmia in patients without PE (9/28, 34.6%). Only 6 (1.6%) patients had a contraindication to pharmacologic thromboprophylaxis, mainly due to thrombocytopenia (5/6, 83.3%). Details about the indications for therapeutic anticoagulation and the contraindications to pharmacologic thromboprophylaxis can be found in Table A1 of the Appendix.

Outcomes are shown in Table 2. Patients intubated for ARDS related to COVID-19 and presenting with PE had significantly fewer ventilator-free days than patients not having PE (median of 3 [0–11] days *versus* 12 [0–19] days; $p < 0.001$). The cumulative frequency and the distribution of ventilator-free days according to the study group are shown in Figs. 1 and 2, respectively. The univariable and multivariable linear regression showed a significant association between PE and ventilator-free days (Table 3).

Patients with PE had longer durations of invasive mechanical ventilation than patients not having PE (median of 18 [11–32.5] *versus* 12 [9–19] days; $p < 0.001$). Mortality at Day-28, and hospital discharge were 22.4% (83/370), and 28.6% (106/370), respectively, and did not differ significantly between groups. The univariable and multivariate logistic regression did not show any association between pulmonary embolism and mortality at day 28 (Appendix: Table A2). Intensive care unit and hospital LOS were significantly longer among patients having a PE ($p < 0.001$). During the study period, 36 patients (9.7%) needed ECMO support. One patient needed VA-ECMO for refractory hypoxemia and hemodynamic instability due to PE and all others were VV-ECMO implanted for refractory hypoxemia. ECMO support tended to be more frequent among patients with PE, although this result was not statistically significant. Patients with PE more frequently

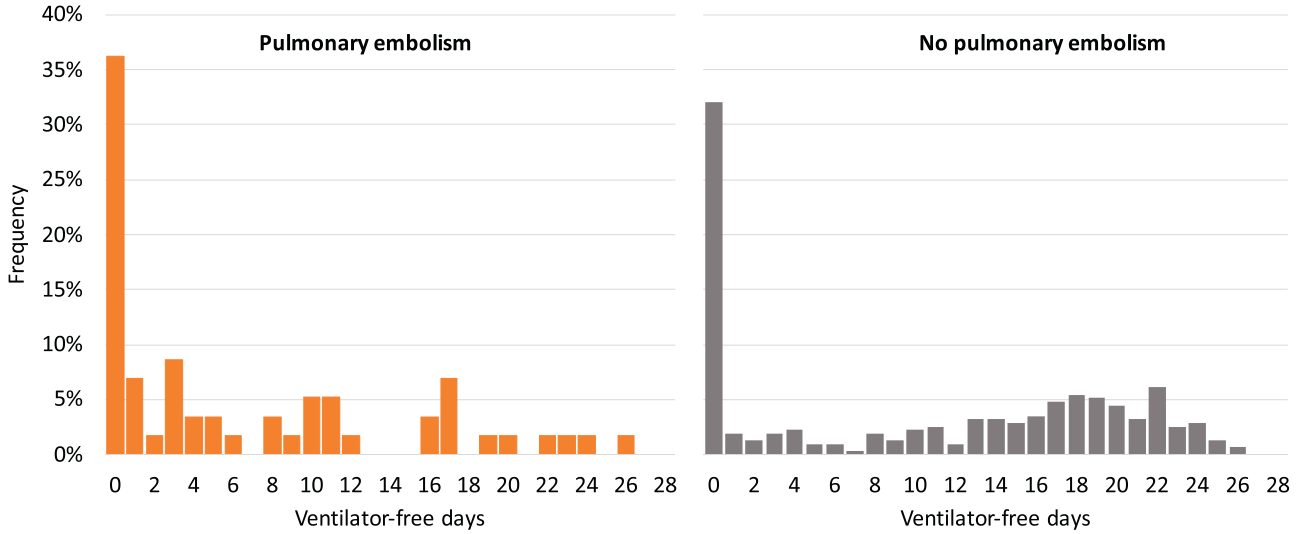

Fig. 2. Distribution of ventilator-free days according to study group.

Table 3
Pulmonary embolism and ventilator-free days.

Univariable analysis, *n* = 370	Ventilator-free days Regression coefficient (95% CI)	*p*-value
No pulmonary embolism	Reference	
Pulmonary embolism	−3.63 (−6.12 to −1.07)	0.006
Multivariable analysis, *n* = 370	**Ventilator-free days Regression coefficient (95% CI)**	***p* value**
No pulmonary embolism	Reference	
Pulmonary embolism	−4.46 (−6.83 to −2.09)	<0.001
SAPS II	−0.08 (−0.14 to −0.03)	0.002
BMI > 30 kg/m2	−0.64 (−2.40 to 1.13)	0.49
Charlson comorbidity index	−1.04 (−1.49 to 0.59)	<0.001

BMI body mass index, *SAPS II* simplified acute physiology score II.

needed inhaled nitric oxide as salvage therapy for hypoxemia. Other ARDS-related adjunctive therapies (prone positioning, and the use of neuromuscular blockade) did not differ between the two groups. Patients with PE presented significantly more ventilatory-associated pneumonia.

A total of 287 (78%) of patients had a screening exam for pulmonary embolism during their stay. Subgroup analysis of these patients confirmed that patients with PE had fewer days alive and free from invasive mechanical ventilation (median of 3 [0−11] days *versus* 12 [0−19] days; $p = 0.02$). Other outcomes were similar to those assessed in the whole study population (Appendix: Table A3).

Subgroup analyses of patients treated with ECMO are shown in Table A4 of the Appendix. We found that PE was associated with longer IMV (median [IQR] days under IMV of 41 [38–63] *versus* 28 [16–41]; $p = 0.02$), and ICU LOS (median of 33 [18.5–42.3] *versus* 27 [16.5–38], a median difference of 6 days; $p = 0.02$). Days alive and free from mechanical ventilation at D-28 were similar among both groups ($p = 0.29$). Despite an absolute difference in mortality of 18.6% (66.7% for patients with PE *versus* 48.1% for patients without PE), this result was non-significant ($p = 0.33$). The duration of ECMO support was not significantly different between groups (median of 34 [18–55] *versus* 21 [14.5–36] days, a median difference of 13 days; $p = 0.12$).

4. Discussion

In this large monocentric observational cohort, our study shows that the occurrence of a PE among patients intubated for ARDS related to COVID-19 was quite frequent and significantly associated with fewer days alive and free of invasive mechanical ventilation. We also found that PE was associated with a longer duration of mechanical ventilation, and longer ICU and hospital LOS. Although statistically non-significant, patients with PE tended to require more frequent ECMO support and longer ECMO support than patients without PE. However, no association was found between the occurrence of PE and mortality.

We identified a high prevalence of PE among intubated patients under invasive mechanical ventilation for ARDS due to COVID-19. Our findings are consistent with data from other smaller cohorts [4,6]. Studies conducted in ICU populations done during the early stage of the pandemic and with limited screening for PE tended to underestimate its prevalence [9,10]. Our study likely provides a more accurate understanding of the true prevalence, as a significant proportion of our patients were screened for PE during their stay. Furthermore, our study is the first to specifically investigate this question among COVID-19 patients with ARDS requiring invasive mechanical ventilation. In comparison to data on patients with non-COVID-19 ARDS, we observed a ten-fold increase in PE prevalence, emphasizing the importance of a low threshold for screening in COVID-19 patients [4,21].

Pulmonary embolism has been shown to increase the need for IMV among patients with severe COVID-19 [11,14]. However, no data existed on its impact on the duration of IMV among patients intubated for ARDS related to COVID-19 with PE. Patients with PE needed also more rescue therapy for refractory hypoxemia. These results certainly indicated greater severity of patients with PE, and probably a longer resolution time of hypoxemia, even if this did not reflect at the time of admission on severity scores or admission PaO_2/FiO_2 ratio. Probably linked with a longer duration of IMV (6 days), patients with PE also significantly developed more VAP, a finding consistent with data published in non-COVID-19 ARDS patients [22].

An increase of almost 5% in-hospital mortality was observed with the occurrence of PE in patients with ARDS due to COVID-19. This difference was not statistically different, most probably reflecting that our study was underpowered to show mortality differences between populations. These results are however in line

with those from other small studies investigating this specific population [23,24].

Our results contrast with the significative association of PE and mortality among patients with severe COVID-19-related pneumonia not hospitalized in the ICU [13]. An explanation for this finding could be that critically ill patients with ARDS have an intrinsically higher mortality making this association more difficult to assess. Another explanation could reside in the distinct pathophysiology of COVID-19-related thrombotic events. Indeed COVID-19 has been shown to induce vascular inflammation and microangiopathy. Post-mortem studies have found a much higher incidence of vascular microthrombi in these patients compared to non-COVID-19 patients with ARDS [25,26]. Thrombi formation directly in the lung, rather than DVT-induced PE, could thus be a specific pathophysiologic feature of COVID-19-related thromboembolic events [27]. This could explain why we found the rate of DVT among critically ill COVID-19 patients presenting with PE was much lower than what we would expect among a general population of critically ill patients with PE [28]. These results are supported by data from smaller observational studies with similar tendencies [3,4]. Interestingly, these findings could explain the diverging results of studies investigating different thromboembolic prophylaxis strategies among ICU and non-ICU patients. Indeed, therapeutic anticoagulation regimens have been shown to reduce mortality among non-ICU patients with severe COVID-19 but not among ICU patients [29,30].

We found that patients treated with corticosteroids or tocilizumab experience higher occurrence of PE. These treatments became standard of care at the end of the first and the second waves, respectively [31,32]. Due to a high workload and less awareness regarding COVID-19-related thrombotic complications at the start of the pandemic, these results might be partly explained by a diagnostic bias. The severity of patients is unlikely to have influenced the differences between the two groups. Indices of severity at ICU admission (SAPS II score, SOFA score, PaO_2/FiO_2 ratio) were not higher among patients with pulmonary embolism, making a treatment bias based on severity less likely. However, the association between corticosteroid use and pulmonary embolism has been described both in COVID-19 and in the general population [33,34]. Concerning tocilizumab, the same association was observed in a multicenter observational study conducted in the early stages of the pandemic [14]. A retrospective observational study also raised safety concerns regarding the use of tocilizumab in COVID-19 patients with PE, as it was associated with increased mortality [35]. Nonetheless, prospective data from large international cohorts are still necessary to address this issue, and direct association cannot be inferred from our data. Moreover, the main randomized controlled trials evaluating the effectiveness of these treatments in COVID-19 did not find any differences in thrombotic adverse events between patients treated with the drug and those given a placebo [31,32].

Our results show an almost two-fold increase in ECMO support among patients with PE and a longer ECMO support of almost 2 weeks. Ventilator-free days were similar among ECMO patients due to a long duration of IMV among both groups. However, we also found an impact of PE on the total duration of IMV, and ICU LOS in these very severe patients. These elements are of high clinical importance since ECMO support has a significant logistic impact on patient care, and its duration is associated with more adverse events [36].

Our study has several limitations. First, its retrospective nature and monocentric location limit the interpretation and generalizability of its results. Our study however offers a comprehensive longitudinal view throughout the whole duration of the COVID-19 pandemic of the effect of PE on patient-centered outcomes among intubated patients with ARDS. Most studies assessing clinical outcomes were indeed published early after the start of the pandemic, had few intubated patients and had short follow-up [4,11–13]. Second, due to its retrospective design our study cannot account for a diagnosis bias of PE, especially during the first period of the study when clinicians had less awareness of the prothrombotic state associated with COVID-19, and when surge capacities were overwhelmed. However, a large proportion of patients not having a PE had a screening with a CTPA during their hospital stay which may limit this bias; our subgroup analysis among patients that had a CTPA during their hospital stay showed the same association between PE and days alive and ventilator-free. Third, the timing of PE occurrence and its effect on outcomes could not be analyzed. However, most of our patients were diagnosed with PE early in the course of the disease possibly limiting its influence on the outcomes. Fourth, our registry does not provide information on other in-hospital complications that could have influenced the outcome. Finally, our study was certainly underpowered to assess the risk of mortality among patients presenting with PE. Further assessment of this outcome would need a multicentric effort in order to guarantee sufficient power.

5. Conclusion

The occurrence of PE was high among patients with ARDS due to COVID-19 and was significantly associated with fewer days alive and free from invasive mechanical ventilation, longer duration of invasive mechanical ventilation, and increased ICU and hospital lengths of stay, but not with higher mortality. Larger prospective cohorts are needed to determine the best preventive strategies in this specific population.

Declarations

Ethics approval and consent to participate

All patients or close relatives were informed that their data were included in this registry. Human research ethics committee approval for the study was the ethical committee of Geneva (BASEC #: 2020-00917) following our local regulations.

Consent for publication

All patients or close relatives were informed that their data might be published.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also

confirm that the personal details of the patients and/or volunteers have been removed.

Disclosure of interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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Author contributions

SP, NS, HW, and TRN had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization: SP, TRN and KB. Data curation and formal analysis: SP, NS, CLT, TRN, HW, and KB. Investigation: SP, CLT, NS. Methodology: SP, TRN, HW. Writing – original draft: SP, NS, CLT, and TRN. Writing – review and editing: SP, HW, JP, and KB. Visualization: SP. Supervision: JP and KB. Funding acquisition: JP.

All authors interpreted the data and critically revised the manuscript for important intellectual content and gave approval for the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The manuscript's guarantors (SP and KB) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2024.101348.

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Discussion

La présente étude observationnelle rétrospective, monocentrique, réalisée sur la base de données COVID-19 du service des soins intensifs des Hôpitaux Universitaires de Genève, a permis de démontrer que la survenue d'une EP est fréquente chez les patients intubés pour un CARDS et de mettre en évidence un impact pronostic significatif associant survenue d'une EP et nombre de jours vivants sans support ventilatoire invasif. Nous avons, en effet, pu démontrer que les patients avec EP, présentaient 9 fois moins de jours (médiane) vivants et sans support de ventilation mécanique invasive que les patients indemnes d'EP. De manière similaire, les durées de séjour aux soins intensifs et hospitalières se retrouvent significativement rallongées en cas de survenue d'une EP. Nous retrouvons également une tendance vers une nécessité plus grande de support par ECMO et des durées de support extracorporel plus longues. Nous n'avons en revanche pas retrouvé d'impact significatif de la survenue d'une EP sur la mortalité de ces patients.

Notre étude met en évidence une prévalence importante de l'EP au sein de cette population de patients critiques, de l'ordre de 16%. Nos résultats concordent avec les données d'études observationnelles de plus petite taille [6, 9]. Les études effectuées dans la phase initiale de la pandémie et ayant une faible proportion de patients correctement dépistés ont eu une tendance à sous-estimer la prévalence de la maladie thromboembolique chez les patients intubés pour un COVID-19 [7, 8]. Notre étude apporte de ce fait un regard probablement plus précis sur la prévalence réelle de cette complication. De plus, notre étude est la première s'est spécifiquement intéresser aux patients présentant les plus graves spectres de la maladie ; les autres études précitées incluant également des patients ne nécessitant pas de ventilation

mécanique invasive. En comparaison avec les quelques données existantes chez les patients présentant un ARDS d'origine autre que le COVID-19, nous observons une augmentation de la prévalence de l'EP de l'ordre de 10, soulignant l'importance du dépistage de celle-ci chez les patients atteints de COVID-19 [5, 6].

Il était déjà bien démontré que la survenue d'une EP augmentait le recours à un support ventilatoire invasif chez des patients hospitalisés hors des soins intensifs avec un COVID-19 sévère [24, 27]. Les études s'intéressant à la sous-population des patients hospitalisés aux soins intensifs se sont, quant à elles, essentiellement intéressées à l'association entre EP et mortalité [9, 24, 27]. Une seule étude observationnelle rapporte des données se référant à d'autres critères de jugement clinique [28]. Toutefois, le but premier de l'étude était la recherche des facteurs de risque de survenue d'une EP et non son influence sur des devenirs cliniques. Les données de cette étude tendent à montrer une durée de ventilation mécanique plus longue, sans effet sur les jours vivants et libres de ventilation mécanique invasive à 28 jours ou sur la mortalité. L'association de l'EP avec une durée de ventilation plus longue n'a toutefois pas été étudiée de manière à ajuster les résultats pour des éventuels facteurs confondants, tels que le score SAPS ou l'indice de masse corporelle. Notre étude analyse quant à elle spécifiquement l'association de la survenue d'une EP sur ces critères cliniques de jugement, jusqu'ici non explorés de manière rigoureuse. Nos résultats indiquent très certainement une plus grande sévérité des patients ayant une EP, ainsi qu'une probable résolution plus lente de l'hypoxémie, alors que cela ne se reflète pas nécessairement sur les scores de gravité ou le rapport PaO_2/FiO_2 à l'admission. Cette augmentation médiane de la durée de ventilation de 6 jours chez les patients ayant une EP est également probablement responsable d'une survenue plus fréquente de pneumonies associées à la ventilation mécanique. En effet, dans des populations non-COVID-

19, la durée de ventilation mécanique a été démontrée comme étant un facteur de risque majeure de survenue de pneumonies associées à la ventilation [29]. Celles-ci sont par ailleurs associées à une morbi-mortalité plus importante [30].

Notre étude ne retrouve cependant pas d'association statistiquement significative entre EP et mortalité. Toutefois, nous remarquons que les patients présentant une EP ont 6% de mortalité en plus que ceux n'en ayant pas au sein de notre cohorte. Bien que cette différence puisse être cliniquement significative, il est fort probable que notre étude ne possède pas la puissance nécessaire pour analyser avec exactitude ce critère de jugement au sein de cette population. Par ailleurs, ces résultats sont dans la même ligne que les données d'autres études portant sur de plus petits échantillons de patients [31, 32]. De plus grandes cohortes multicentriques seront nécessaires afin de pouvoir analyser plus précisément l'association entre la survenue d'une EP et la mortalité.

Les études ayant analysé des populations de patients présentant un COVID-19 sévère hospitalisés à l'étage ou dans une unité de soins continus ont quant à elles démontré un impact sur la mortalité de la survenue d'une EP [26]. Nos résultats contrastent avec ceci et plusieurs explications peuvent être évoquées. Premièrement, la sévérité plus grande des patients hospitalisés aux soins intensifs leur confère intrinsèquement un risque de mortalité plus grand, rendant cette association plus difficile à évaluer. En effet, afin de détecter une différence de mortalité cliniquement significative, un échantillon plus grand de patients sera alors nécessaire. Une seconde explication pourrait résider dans la physiopathologie distincte de la coagulopathie associée au COVID-19 [12]. Les études post-mortem ont en effet identifié une présence accrue de microthrombi dans la vascularisation pulmonaire des patients souffrant

d'un CARDS en comparaison avec des patients ayant un ARDS d'autre étiologie [33-35]. Ainsi, la formation de thrombi au sein de la vascularisation pulmonaire, favorisée par les lésions alvéolaires et endothéliales dues au virus, plutôt qu'un modèle thrombo-embolique veineux classique, pourrait être un trait physiopathologique distinct, ou du moins exacerbé, du COVID-19 [36]. Ceci pourrait également expliquer le fait que le taux de thromboses veineuses profondes identifiées chez les patients souffrant d'une EP est bien moindre que celui attendu au sein d'une population non sélectionnée de patients de soins intensifs souffrant d'une EP [37, 38]. Cette tendance à retrouver moins de thromboses veineuses profondes chez les patients COVID-19 souffrant d'EP est par ailleurs soutenue par des données de plus petites études observationnelles [6, 39].

De manière intéressante, cette physiopathologie distincte du COVID-19 pourrait en partie expliquer les résultats divergents des études portant sur les régimes de thromboprophylaxie entre les patients hospitalisés aux soins intensifs et ceux pris en charge dans d'autres unités de soins. Il a en effet été démontré qu'une thromboprophylaxie par anticoagulation thérapeutique diminuait la mortalité des patients hospitalisés hors des unités de soins intensifs [40, 41]. Toutefois, une étude randomisée contrôlée multiplateforme n'a pas montré un bénéfice similaire au sein d'une population de patients de soins intensifs, et a même soulevé la possibilité d'un effet délétère d'une telle pratique [42]. La formation de ces microthrombi au sein de la vascularisation pulmonaire seraient dès lors un aspect soulignant la gravité de l'atteinte respiratoire liée au COVID-19. Nos résultats soulignent pourtant l'importance de poursuivre la recherche clinique dans ce domaine, afin de diminuer l'incidence de l'embolie pulmonaire et son influence sur la durée de ventilation de ces patients et sur le recours à des thérapies de secours.

De manière intéressante, les patients atteints d'une EP ont reçu significativement plus de corticoïdes et de tocilizumab pour le traitement du COVID-19. Ces thérapies sont devenues des standards de soins respectivement au début et à la fin de la deuxième vague [43, 44]. Par conséquent, nous retrouvons une grande hétérogénéité de l'utilisation de ces traitements lors des première et deuxième vagues (Tableau 1), ce qui peut induire un biais important dans l'interprétation de ces résultats. De plus, en raison de la surcharge de travail engendrée par l'afflux de patients et d'une moindre prise de conscience de l'état prothrombotique associé au COVID-19 au cours des premiers mois de la pandémie, les cliniciens ont possiblement moins dépisté l'EP. En effet, dans notre cohorte, durant la première vague, la proportion de patients ayant eu un dépistage de l'EP est moindre que lors des vagues suivantes où quasiment tous les patients ont eu un scanner thoracique injecté durant leur séjour, influençant ainsi probablement la prévalence de l'EP (Tableau 2). L'association de ces deux éléments est possiblement responsable d'un biais diagnostique. Par ailleurs, une différence de sévérité des patients entre les deux groupes n'est probablement pas responsable de cette association entre l'administration de ces traitements et la survenue d'une EP. En effet, les indices de sévérité (score SAPS II, score SOFA, rapport PaO_2/FiO_2) à l'admission entre les patients ayant eu une EP et ceux n'en ayant pas eu étant similaires, un biais d'administration des traitements semble exclu. A noter qu'une oxygénothérapie aux lunettes de plus de 2 litres par minutes était le critère afin d'administrer ces traitements, rendant nos patients virtuellement tous candidats à ces thérapies).

Tableau 1. Proportions de patients traités par corticostéroïdes ou tocilizumab pour une infection COVID-19 selon les périodes précoces ou plus tardives de la pandémie.

	Wave 1 (n=124)	**Subsequent waves (n=246)**
Corticosteroids for COVID-19, n (%)	0 (0)	234 (95.1)
	Waves 1 and 2 (n=246)	**Subsequent waves (n=124)**
Tocilizumab, n (%)	0 (0)	91 (73.4)

Tableau 2. Prévalence de l'embolie pulmonaire et taux de dépistage par scanner thoracique injecté selon les vagues épidémiques.

	Pulmonary embolism, n (%)	**CTPA, n (%)**
First wave (n=124)	7 (5.6)	61 (49.2)
Subsequent waves (n=246)	51 (20.7)	226 (91.9)

Cependant, lorsque l'on ne considère que les patients ayant été dépistés pour une EP pendant leur séjour, cette différence significative de proportions de patients traités par des corticoïdes ou tocilizumab pour le COVID-19 persistait, parlant en défaveur du seul effet d'un biais diagnostique. L'association entre les traitements par corticostéroïdes et la survenue d'une EP a été déjà largement décrite, aussi bien dans des populations de patients souffrant du COVID-19 que dans la population générale [45, 46]. Une étude observationnelle multicentrique, effectuée au début de la pandémie, retrouvait également des données similaires concernant l'association entre le traitement par tocilizumab et la survenue d'EP [27]. Une autre étude soulève quant à elle des doutes quant à la sécurité de ce traitement en lien avec la survenue d'événements thrombo-emboliques [47]. Il semble cependant difficile d'affirmer qu'une telle association existe belle et bien sur la base de notre cohorte et il n'existe pour l'heure pas de données probantes issues de larges échantillons la soutenant. De plus, les principales études

randomisées contrôlées testant l'effet des corticostéroïdes ou du tocilizumab chez les patients atteints de COVID-19 ne rapportent pas spécifiquement le nombre d'EP survenues dans leurs données de suivi [43, 44, 48, 49]. Toutefois, dans ces grandes cohortes, les événements indésirables rapportés ne diffèrent pas entre les patients traités par placebo ou tocilizumab, laissant suggérer une absence d'effet significatif de ces médicaments sur la survenue d'un événement thrombo-embolique.

Au sein de notre cohorte, nous retrouvons pratiquement un doublement de la nécessité de soutient par ECMO chez les patients présentant une EP en comparaison avec ceux n'en n'ayant pas. De plus, la durée de soutien par ECMO se retrouve grandement augmentée, de près de 2 semaines. Bien que ces résultats ne soient pas statistiquement significatifs, probablement en raison du petit nombre de patients ayant bénéficié d'une ECMO, ils sont cliniquement importants. En effet, le soutien par ECMO a un impact logistique majeur au sein d'un service de soins intensifs et il a été clairement démontré que la durée de soutien extracorporelle était directement corrélée aux effets indésirables de la thérapie [50]. Nous n'avons par ailleurs pas retrouvé de différence de jours vivants et libres de ventilation mécanique invasive entre les patients ayant eu une embolie pulmonaire et ceux n'en n'ayant pas eu au sein de cette sous-population. Ceci vient probablement du fait que les durées médianes de ventilation mécanique invasive sont très longues chez ces patients, rendant nuls les jours vivants et libres de ventilation mécanique à 28 jours de l'admission. Par ailleurs, la durée de séjour aux soins intensifs se retrouve significativement prolongée chez les patients sous ECMO ayant eu une EP, probablement en lien avec une sévérité plus grande, mais possiblement aussi par un biais de survie, la mortalité de ces patients étant, de manière surprenante, légèrement plus faible que celles des patients n'ayant pas eu d'embolie pulmonaire.

Notre étude comporte plusieurs limites. Premièrement, sa nature rétrospective et monocentrique limite l'interprétation et la généralisation de ses résultats. De plus, l'inclusion de patients tout au long de la période de pandémie ne permet pas de tenir compte de l'évolution des prises en charges au cours du temps, notamment en termes de thérapeutique que de sélection des patients admis aux soins intensifs. Toutefois, la majorité des études observationnelles s'intéressant à l'impact de la survenue d'une EP ont été publiées au début de la pandémie, ne comprennent qu'un petit nombre de patients et évaluent principalement la mortalité à court terme [6, 24-26]. Notre étude quant à elle permet une visualisation plus globale de l'impact de la survenue d'une EP au sein de cette population de patients critiques et ce, sur des critères de jugement clinique plus larges. Deuxièmement, du fait de son design rétrospectif, nous ne pouvons pas exclure un biais lié au diagnostic de l'EP. Ceci est particulièrement vrai durant la première phase de la pandémie, lorsque les cliniciens étaient moins conscients du risque thrombotique lié au COVID-19 et lorsque les capacités d'accueil en soins intensifs ont dû être ajustées rapidement pour faire face à l'afflux de patients [1]. Ce biais a toutefois été probablement limité par le fait qu'une grande proportion (plus de 70%) des patients classifiés dans le groupe n'ayant pas eu d'EP ont eu un scanner thoracique de dépistage durant leur séjour. Par ailleurs, notre analyse de sous-groupe intégrant uniquement les patients ayant eu un scanner de dépistage durant leur séjour retrouve la même association statistique entre survenue d'une EP et jours vivants et libres de ventilation mécanique invasive. Troisièmement, nous n'avons pas pu analyser l'effet du timing de la survenue de l'EP sur les devenirs cliniques. Cependant, la majorité de nos patients a eu un diagnostic précoce d'EP, limitant ainsi l'éventuelle influence temporelle de l'événement thromboembolique sur les outcomes évalués. Nous pouvons également soulever que notre registre ne permet pas de

tenir compte d'éventuelles autres complications pouvant survenir durant le séjour et ayant pu influencer le devenir des patients. Finalement, notre étude manque certainement de puissance afin de pouvoir clairement analyser l'effet de l'EP sur la mortalité des patients présentant un CARDS. Une analyse plus poussée de cette association nécessiterait un effort multicentrique, afin d'assurer une puissance suffisante de l'analyse statistique.

Les résultats amenés par notre étude peuvent s'avérer être d'une grande importance pour le clinicien, puisque la survenue d'une complication telle que l'EP peut être perçue comme un élément de gravité supplémentaire qui peut éventuellement mener à un changement d'objectif de soins et, par exemple, à une limitation ou un retrait thérapeutique. Nos données tendent à montrer que les patients présentant une EP ont certes un impact sur leur séjour aux soins intensifs, notamment en termes de durée de ventilation mécanique invasive, de recours à un soutient extracorporel et de durée de séjour, mais que leur mortalité hospitalière ne s'en voit pas affectée. De ce fait, une telle décision de changement d'objectif de soins ne devrait pas être prise sur la seule base de la survenue d'une complication thromboembolique durant le séjour.

Pour conclure, nous pouvons dire que la prévalence de l'EP au sein d'une population de patients hospitalisés aux soins intensifs et intubés pour un CARDS est grande et de l'ordre de 16%. La survenue d'une EP chez ces patients est significativement associée à moins de jours vivants et libres de ventilation mécanique invasive durant les 28 premiers jours de prise en charge aux soins intensifs. Cet effet est principalement dû à une durée de ventilation mécanique invasive plus longue et non à une mortalité plus élevée. Les patients intubés pour un CARDS présentant une EP tendent à nécessiter plus fréquemment un soutient respiratoire

extracorporel et, lorsque celui-ci est requis, pour une plus longue durée. Toutefois, même au sein de cette population des patients les plus graves, la mortalité n'est pas plus élevée chez les patients présentant une EP. Ces résultats soulignent l'importance de ne pas nécessairement prendre en compte la survenue d'une EP dans un processus décisionnel de changement d'objectif de soins et ouvrent par ailleurs la voie vers l'analyse de l'impact de ces événements thromboemboliques sur cette population à plus long terme, notamment en termes d'atteinte fonctionnelle, de troubles neuropsychologiques et de syndrome de stress post-traumatique, questions auxquelles notre registre pourra peut-être contribuer à répondre.

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