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Original article

# Pulmonary embolism severity and in-hospital mortality: An international comparative study between COVID-19 and non-COVID patients

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ABSTRACT

*Objective:* To compare the severity of pulmonary embolism (PE) between patients with and without COVID, and to assess the association between severity and in-hospital-mortality.
*Methods:* We performed an analysis of 549 COVID (71.3% PCR-confirmed) and 439 non-COVID patients with PE consecutively included by 62 Spanish and 16 French emergency departments. PE-severity was assessed by size, the presence of right ventricular dysfunction (RVD), and the sPESI. The association of PE-severity and in-hospital-mortality was assessed both in COVID and non-COVID patients, and the interaction of COVID status and PE severity/outcome associations was also evaluated.
*Results:* COVID patients had PEs of smaller size (43% vs 56% lobar or larger, 42% vs. 35% segmental and 13% vs. 9% subsegmental, respectively; $p = 0.01$ for trend), less RVD (22% vs. 16%, $p = 0.02$) and lower sPESI ($p = 0.03$ for trend). Risk of in-hospital death was higher in COVID patients (12.8% vs. 5.3%, $p < 0.001$). PE-severity assessed by RVD and sPESI was independently associated with in-hospital-mortality in COVID patients, while PE size and sPESI were significantly associated with in-hospital-mortality in non-COVID. COVID status showed a significant interaction in the association of PE size and outcome ($p = 0.01$), with OR for in-hospital mortality in COVID and non-COVID patients with lobar or larger PE of 0.92 (95%CI=0.19–4.47) and 4.47 (95% CI=1.60–12.5), respectively. Sensitivity analyses using only PCR-confirmed COVID cases confirmed these results.
*Conclusion:* COVID patients present a differential clinical picture, with PE of less severity than in non-COVID patients. An increased sPESI was associated with the risk of mortality in both groups but, PE size did not seem to be associated with in-hospital mortality in COVID patients.

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## 1. Introduction

Infection by SARS-Cov-2 is mainly characterized by fever and respiratory symptoms, with dyspnea and lung infiltrates in more severe cases[1,2]. Many patients also present a procoagulant state, which is biochemically detected by increased D-dimer levels and is related to complications and a worse prognosis[1]. Accordingly, some authors have suggested that pulmonary embolism (PE) is more common in patients with COVID-19 than in the uninfected population[3–7]. A recent meta-analysis of 66 studies that included 23,117 COVID patients that had been hospitalized reported a PE prevalence rate of 7.8% (95% confidence interval [CI]=6.2–9.4)[8].

Nonetheless, the severity of PE in COVID patients remains to be established. On one hand, the size of the pulmonary arteries in which PE occurs in COVID patients does not seem to be as large as in PE in non COVID patients, although this has not been properly assessed. Although only a small fraction of PEs (8%) was reported as subsegmental in the previously commented meta-analysis [8], other case series reported that in more than half of PEs in COVID patients the size of the involved arteries was segmental at most [9,10]. PEs associated with COVID may result from a hyperinflammatory state that leads to a pro-coagulant state, whereas in non-COVID patients PEs are often subsequent to a deep venous thrombosis (DVT), which may be of larger size. On the other hand, the frequency of right ventricular dysfunction (RVD) in large series of COVID patients with PE has not been previously described, and classification using classical indexes, such as the simplified Pulmonary Embolism Severity Index (sPESI) score, has seldom been reported. Finally, it is not yet known how all these PE severity markers correlate with COVID patient outcome. In non-COVID patients, it is well described that patients with subsegmental PEs have a very low mortality risk, while the presence of a RVD is associated with worse prognosis[11]. Bearing in mind all these gaps in the current knowledge, the present large, retrospective international, multicenter study aimed to describe differences in PE severity between COVID and non-COVID patients. The secondary objective was to investigate whether there are significant relationships between the estimated PE severity and mortality in COVID and non-COVID patients and if these relationships differ between these two groups of patients.

## 2. Methods

### 2.1. Study design and setting

This is an ancillary analysis of two retrospective large cohorts. On one hand, the SIESTA cohort is a multipurpose Spanish cohort generated by 62 EDs that included all COVID patients diagnosed with 1 of the 10 unusual manifestations subject to investigation as well as randomly selected non-COVID patients with the same manifestation included as controls. One of these manifestations was PE, and all COVID and non-COVID patients diagnosed with PE by a computed tomographic pulmonary angiogram (CTPA) form this cohort were included in the present study, irrespective of the severity of PE and the patient hemodynamic status. The COVID patients with PE included in the present analysis were recruited in the 62 EDs during March-April 2020 (during the first wave of the COVID pandemic), while and non-COVID patients with PE were recruited during the same period (first wave) as well as during March-April 2019 (one year before the COVID pandemic). Extensive details of the SIESTA protocol have been extensively described elsewhere [12–14]. On the other hand, the PEPCOV cohort is an international cohort (with the participation of 26 centers from France, Spain, Italy, Belgium, Chile and Canada) that included all patients in whom a CTPA was performed during patient evaluation in the Emergency Department (ED) between February 1 to April 10, 2020. All COVID and non-COVID patients included in the PEPCOV registry coming from the 16 French EDs with a final diagnosis of PE based on CTPA findings were included in the present analysis, irrespective of the severity of PE and the patient hemodynamic status. Extensive details of the PEPCOV protocol and have been extensively described elsewhere[7,15,16].

COVID diagnosis was made based on SARS-CoV-2 RNA detection in a nasopharyngeal swab by reverse transcriptase polymerase chain reaction (RT-PCR). Spanish and French hospitals experienced a huge shortage of tests to confirm SARS-CoV-2 infection during several weeks of the first wave of the COVID-19 pandemic[17,18], and therefore, COVID diagnosis was also accepted in the epidemiological context of the first COVID pandemic wave by the presence of a clinically compatible clinical picture of SARS-CoV-2 infection (including at least malaise, fever and cough) and a CTPA with typical findings (i.e. bilateral interstitial lung ground-glass infiltrates, peripheral consolidations, or crazy-paving).

### 2.2. PE diagnosis and severity assessment

All CTPA were requested by ED physicians. Every diagnosis of PE was confirmed by a senior radiologist at a local level.

The severity of PE was estimated in three different ways. First, according to PE size, that was classified by the localization (or "size") of the most proximal artery involved: (1) lobar, defined when lobar or larger arteries were involved; (2) segmental, defined when only segmental with or without subsegemental arteries were involved, and (3) subsegmental, when PE was limited to subsegmental arteries. Second, according to the presence of RVD in the CTPA, defined as a right ventricle / left ventricle diameter ratio $\geq 1$. And third, the sPESI score was calculated in every patient based on retrospective chart review[19]. We also recorded a concomitant diagnosis of deep venous thrombosis (DVT) in patients coming from the SIESTA cohort (as this data had not been recorded in patients coming from the PEPCOV cohort).

### 2.3. Independent variables

The following data were collected from patients in the two registries: nine baseline characteristics (demographic: age, sex; comorbidity: hypertension, chronic heart failure, chronic renal disease; risk factors for PE: active cancer, previous DVT, immobilization or surgery the previous 30 days and treatment with estrogens) and 12 clinical characteristics of the index episode (clinical manifestations: shortness of breath, chest pain, leg pain/edema, hemoptysis, length of symptoms; vitals at ED arrival: systolic blood pressure, heart rate, pulse oxymetry, temperature; analytical findings: D-dimer, C- reactive protein –CRP-, leukocytes).

### 2.4. Outcome

Patients were followed until hospital discharge. The outcome considered in the present study was in-hospital all-cause mortality that was adjudicated at a local level. At the time of performing the present analysis, all patients had finished the index episode (i.e., they had been discharged home or had died during hospital admission).

### 2.5. Statistical analysis

Continuous variables were presented as median (interquartile range –IQR-) and discrete variables as absolute values and percentages. The characteristics of COVID and non-COVID patients were compared with the non-parametric Mann-Whitney test and the chi-square test for continuous and discrete variables, respectively. When discrete variables represented an ordinal variable, chi-square for trend was used.

Associations with in-hospital mortality were tested for PE size (dichotomized as lobar vs. segmental/subsegmental), the presence of RVD, and sPESI (dichotomized as 0 vs. $\geq 1$ points) and expressed as odds ratio (OR) with 95% CI, first unadjusted, and then progressively adjusting the OR (aOR) for baseline patient characteristics (model A), clinical characteristics of the index episode (model B) and by both types of characteristics (model C, fully adjusted). For the adjusted models, we

created 10 datasets in which missing values in the covariates were replaced by imputed values using the multiple imputation technique provided by SPSS software, which is based on random drawings of imputed data from a Bayesian posterior distribution, and we used Mersenne twister as pseudorandom number generator and 2000,000 as seed. In the fully adjusted model, we checked the existence of a first-order interaction of COVID status in the associations between PE severity markers and outcomes. Analyses regarding the sPESI score and its association with COVID status and outcomes were only reported unadjusted, because most of the items used for adjustment are comprised in the sPESI score itself. As sensitivity analysis, we repeated all calculations using only including in the COVID group those patients with PCR confirmation of -SARS-CoV-2 infection. Statistical significance of differences between groups was accepted if $p < p < 0.05$ or the 95%CI of the OR excluded the value 1. The SPSS v.25 (IMB, Armonk, NY, USA) and InStat v 3.0 (GraphPad Software, San Diego, CA, USA) packages were used for statistical calculations.

### 2.6. Ethics

The SIESTA cohort was approved by the Ethics Committee of the Hospital Clínic of Barcelona (Spain; reference number HCB/2020/0534) and the PEPCOV cohort by the Steering Committee of *Assistance Publique–Hôpitaux de Paris*. Due to the retrospective, non-interventional nature of the cohorts, and the urgent need for information during the first wave of the COVID pandemic, informed consent was waived in all the participating centers of the two cohorts. The present study was carried out in strict compliance with the principles of the Declaration of Helsinki.

## 3. Results

The present analysis included 988 patients with PE, with the SIESTA cohort providing 677 patients from 62 Spanish EDs, and the PEPCOV cohort providing 311 patients from 16 French EDs. The median age was 67 years (IQR 54–78), and 46.5% were females. Of these, 549 were COVID patients (SIESTA: 339; PEPCOV: 210), and 439 were non-COVID patients (SIESTA: 338; PEPCOV: 101). SARS-CoV-2 infection was microbiologically confirmed by RT-PCR in 71.3% of COVID patients (SIESTA: 72.8%, PEPCOV: 66.0%; $p = 0.196$). Compared to non-COVID patients with PE, COVID patients with PE were younger, more frequently males, risk factors for PE were less frequent, and symptom duration was longer before ED consultation, and they had less leg pain/edema, lower systolic blood pressure and pulse oxymetry and a higher temperature and CRP values (Table 1). A concomitant diagnosis of DVT was made in 38.1% of COVID patients with PE and in 17.5% of non-COVID patients with PE ($p < 0.001$).

In patients with COVID, PEs were of more distal topography compared to non-COVID patients: 43% lobar, 44% segmental and 13% sub-segmental vs. 56%, 35% and 9%, respectively ($p < 0.001$ for trend, Table 2). PEs were lobar or larger in 189 COVID patients (43%) and in 241 non-COVID patients (56%) (difference 13%, 95%CI 7% to 19%, $p < 0.001$, Table 2). The presence of RVD on CTPA was less frequent in COVID patients compared to non-COVID patients: 22% vs. 16% (difference 6%, 95%CI 1% to 10%, $p = 0.026$). COVID patients had a significantly lower sPESI score than non-COVID patients ($p = 0.033$ for trend, Table 2). Similar results were obtained in the sensitivity analysis including only COVID cases confirmed by PCR, although the lower sPESI score in COVID group did not reach statistical significance (Table 2).

Eighty-five patients died during hospitalization (8.6%), and the risk of in-hospital death was higher in COVID patients (56 deaths, 12.8%) than in non-COVID patients (29 deaths, 5.3%; difference 7%, 95%CI 4% to 11%, $p < 0.001$; Fig. 1). In-hospital mortality was always higher in COVID patients in all subgroup analyses based on PE size, DVD and sPESI score, and these differences were always statistically significant, with the exception of patients with PE size that was lobar or larger ($p = 0.151$) and patients with a sPESI score of >2 points ($p = 0.055$, Fig. 1).

Regarding the relationship between PE severity and outcome,

**Table 1**
Clinical characteristics of patients with pulmonary embolism included in the present study.

| Baseline characteristics | Total($N = 988$)*n* (%) | Missing values*n* (%) | COVID($N = 439$)*n* (%) | Non-COVID($N = 549$)*n* (%) | *p* |
|---|---|---|---|---|---|
| **Demographic data** | | | | | |
| Age (years) [median (IQR)] | 67 (54–78) | 0 (0) | 65 (54–77) | 65 (54–80) | **0.046** |
| Sex female | 459 (46.5) | 0 (0) | 177 (40.3) | 282 (48.6) | **0.001** |
| **Comorbidity** | | | | | |
| Hypertension | 463 (46.9) | 1 (0.1) | 199 (45.3) | 264 (48.2) | 0.373 |
| Chronic heart failure | 66 (6.7) | 1 (0.1) | 24 (5.5) | 42 (7.7) | 0.170 |
| Chronic renal disease | 41 (4.3) | 1 (0.1) | 19 (4.3) | 22 (4.0) | 0.806 |
| **Risk factors for pulmonary embolism** | | | | | |
| Active cancer | 171 (17.3) | 1 (0.1) | 49 (11.2) | 122 (22.3) | **<0.001** |
| Previous deep venous thrombosis | 137 (13.9) | 2 (0.2) | 28 (6.4) | 109 (19.9) | **<0.001** |
| Immobilization/Surgery the previous month | 100 (10.1) | 2 (0.2) | 40 (9.1) | 60 (10.9) | 0.348 |
| On estrogen treatment | 31 (3.1) | 1 (0.1) | 6 (1.4) | 25 (4.6) | **0.004** |
| **Clinical characteristics of the index episode** | | | | | |
| **Clinical manifestations** | | | | | |
| Shortness of breath | 701 (71.0) | 0 (0) | 323 (73.6) | 378 (68.9) | 0.104 |
| Chest pain | 342 (34.7) | 1 (0.1) | 140 (32.0) | 202 (36.8) | 0.113 |
| Leg pain/edema | 218 (22.1) | 1 (0.1) | 56 (12.8) | 162 (29.5) | **<0.001** |
| Hemoptysis | 29 (2.9) | 2 (0.2) | 12 (2.7) | 17 (3.1) | 0.738 |
| Length of symptoms (days) [median (IQR)] | 4 (1–10) | 31 (3.1) | 7 (3–13) | 3 (1–7) | **<0.001** |
| **First vitals at emergency department arrival** | | | | | |
| Systolic blood pressure (mmHg) [median (IQR)] | 130 (116–147) | 2 (0.2) | 129 (113–142) | 133 (118–150) | **<0.001** |
| Heart rate (bpm) [median (IQR)] | 93 (80–110) | 2 (0.2) | 93 (82–110) | 93 (79–110) | 0.262 |
| Pulse oxymetry (%)[median (IQR)] | 95 (92–97) | 11 (1.1) | 95 (91–97) | 96 (93–98) | **<0.001** |
| Temperature ( °C) [median (IQR)] | 36.5 (36.0–37.1) | 4 (0.4) | 36.6 (36.0–37.3) | 36.5 (36.0–37.0) | **0.010** |
| **Analytical findings** | | | | | |
| D-dimer (ng/mL)[median (IQR)] | 4526 (1765–10,000) | 156 (15.8) | 5024 (1760–13,237) | 4340 (1771–8890) | 0.114 |
| CRP (mg/dL) [median (IQR)] | 53 (16–122) | 148 (15.0) | 84 (29–164) | 31 (11–86) | **<0.001** |
| Leucocytes (cells/μL) [median (IQR)] | 9.2 (7.0–11.9) | 11 (1.1) | 9.5 (6.9–12.1) | 9.0 (7.2–11.5) | 0.409 |

*$P$ calculated by chi-square for trend for qualitative variables, and by linear regression for quantitative variables
Bold numbers denote statistical significance ($p < 0.05$)
RVD: right ventricular dysfunction; CRP: C-reactive protein; IQR: interquartile range

**Table 2**
Severity of patients with pulmonary embolism included in the present study.

| | **Total**(*N* =988)*n* (%) | **COVID(all clinically diagnosed)**(*N* =439)*n* (%) | **COVID(only PCR-confirmed)** (*N* =308)*n* (%) | **Non-COVID**(*N* =549)*n* (%) | *p* value* | *p* value** |
|---|---|---|---|---|---|---|
| **According to the size of the pulmonary embolism** | | | | | **<0.001*** ** | **<0.001** |
| Only subsegmental | 105 (10.6) | 56 (12.8) | 39 (12.7) | 49 (8.9) | | |
| Segmental at most | 386 (39.1) | 194 (44.2) | 142 (46.1) | 192 (35.0) | | |
| Lobar or larger | 497 (50.3) | 189 (43.1) | 127 (41.2) | 308 (56.1) | | |
| **According to the presence of right ventricular dysfunction** | | | | | **0.026** | **0.12** |
| No | 795 (80.5) | 367 (83.6) | 262 (85.1) | 428 (78.0) | | |
| Yes | 193 (19.5) | 72 (16.4) | 46 (14.9) | 121 (22.0) | | |
| **According to the simplified PESI score** | | | | | **0.033***** | 0.144 |
| 0 points | 388 (39.3) | 178 (40.5) | 124 (40.3) | 210 (38.3) | | |
| 1 point | 372 (37.7) | 178 (40.5) | 120 (39.0) | 194 (35.3) | | |
| 2 points | 173 (17.5) | 64 (14.6) | 49 (15.9) | 109 (19.9) | | |
| >2 points | 55 (5.6) | 19 (4.3) | 15 (4.9) | 36 (6.6) | | |

Bold numbers denote statistical significance ($p < 0.05$)
* $p$ value refereed to comparison between COVID patients (all clinically diagnosed) and non-COVID patients.
** $p$ value refereed to comparison between COVID patients (only PCR-confirmed) and non-COVID patients.
*** $p$ value calculated by chi-square for trend for qualitative variables

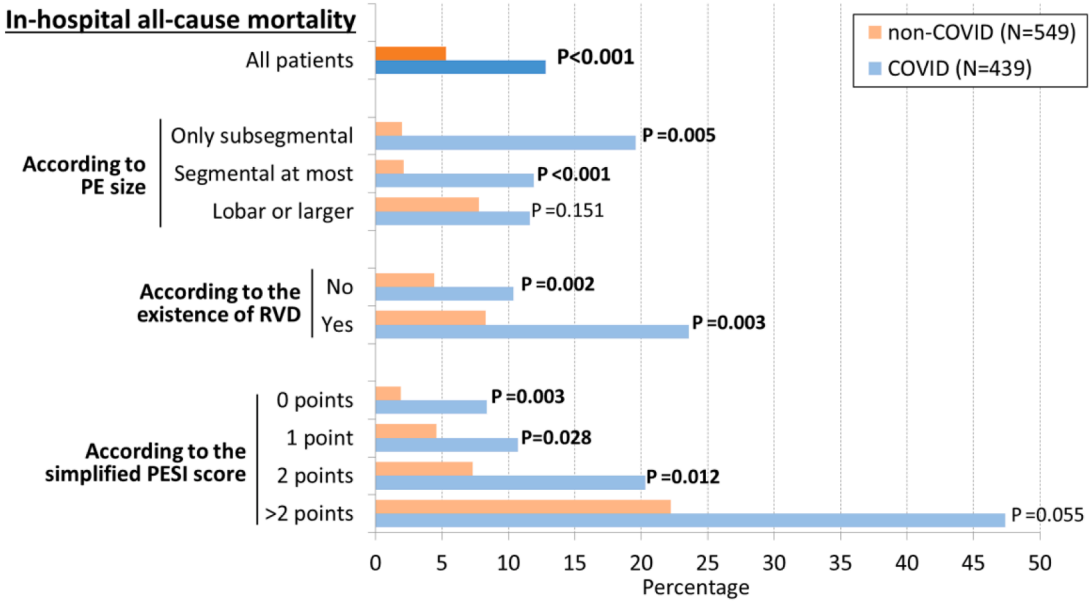


**Fig. 1.** Comparison of outcomes between COVID and non-COVID patients with pulmonary embolism, overall and according to the severity of pulmonary embolism (assessed by pulmonary embolism size, the existence of right ventricular dysfunction and the simplified Pulmonary Embolism Severity Index [PESI] score)
PE: pulmonary embolism; RVD: right ventricular dysfunction
Bold numbers denote statistical significance ($p < 0.05$).

independent predictors of in-hospital mortality were RVD in COVID patients (aOR=3.4, 95%CI=1.5–7.5) and lobar PE size in non-COVID patients (aOR for PE lobar or larger =5.0, 95%CI=1.6–16.4) (Table 3). Additionally, a sPESI score >0 was associated with increased in-hospital mortality in both COVID and non-COVID patients (OR=2.03, 95%CI=1.08–3.78, and OR=4.10, 95%CI=1.41–11.95; respectively) (Table 3). Results obtained in the sensitivity analysis confirmed all these findings (Table 3). COVID status exhibited significant interaction in the relationship between PE size and outcome ($p$ =0.01), but not in the relationship between RVD or sPESI and outcome ($p$ =0.641 and $p$ =0.265, respectively, Fig. 2). Similar results were obtained in the sensitivity analysis, with $p$ values for interaction of 0.041, 0.505 and 0.255, respectively.

A significant increase of risk of in-hospital mortality in both COVID and non-COVID patients was observed as the number of severity markers (lobar or larger PE, RVD, sPESI score >0) increased, with mortality rising from 8.7% in COVID patients with no severity marker to 24.2% when the three markers were present ($p$ =0.022; from 12.3% to 38.1% in the sensitivity analysis using only COVID patients confirmed by PCR; $p$ =0.020), and from 0% to 11.7%, respectively, in non-COVID patients ($p$ <0.001, Table 4). The $p$ value for interaction of COVID status with the relationship between number of severity markers and outcome was 0.06 (0.10 in the sensitivity analysis).

## 4. Discussion

In this retrospective analysis of Spanish and French cohorts of patients diagnosed with PE in the ED during the first wave of the COVID-19 pandemic, PE severity differed between COVID and non-COVID patients, with the former presenting PEs of lower severity. This study confirms that a higher sPESI score was associated with a higher risk of in-hospital mortality in both groups. However, PE topography did not

**Table 3**
Unadjusted and adjusted in-hospital all-cause mortality according to the severity of pulmonary embolism (assessed by the size of the pulmonary embolism, the presence of right ventricular dysfunction and the simplified Pulmonary Embolism Severity Index (PESI) score in COVID and non-COVID patients.

| | **COVID patients (all clinically diagnosed)**Odds Ratio (95% CI) | **COVID patients (only PCR-confirmed)**Odds Ratio (95% CI) | **Non-COVID patients**Odds Ratio (95% CI) |
|---|---|---|---|
| **According to the size of pulmonary embolism** | | | |
| Segmental/ subsegmental | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Lobar or larger | | | |
| Unadjusted | 1.182 (0.757–1.847) | 1.327 (0.827–2.128) | **3.989 (1.499–10.616)** |
| Adjusted (model A, adjusted by baseline characteristics) | 1.101 (0.701–1.728) | 1.275 (0.793–2.052) | **4.459 (1.627–12.219)** |
| Adjusted (model B, adjusted by clinical characteristics of episode) | 1.265 (0.787–2.033) | 1.475 (0.885–2.458) | **3.516 (1.213–10.198)** |
| Adjusted (model C, fully adjusted) | 1.224 (0.758–1.979) | 1.471 (0.879–2.463) | **5.042 (1.551–16.384)** |
| **According to the existence of right ventricular dysfunction in CTPA** | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | | | |
| Unadjusted | **2.600 1.375–4.916)** | **2.017 (1.205–3.377)** | 1.939 (0.877–4.290) |
| Adjusted (model A, adjusted by baseline characteristics) | **3.346 (1.670–6.704)** | **2.059 (1.223–3.468)** | 2.227 (0.972–5.106) |
| Adjusted (model B, adjusted by clinical characteristics of episode) | **2.438 (1.174–5.064)** | **1.895 (1.096–3.275)** | 1.518 (0.643–3.873) |
| Adjusted (model C, fully adjusted) | **3.378 (1.519–7.513)** | **1.961 (1.123–3.424)** | 1.861 (0.723–4.791) |
| **According to the simplified PESI score** | | | |
| 0 points | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| ≥1 points | | | |
| Unadjusted* | **2.025 (1.084–3.784)** | **2.232 (1.292–3.857)** | **4.100 (1.406–11.954)** |

CTPA: computerized tomography pulmonary angiogram, ICU: intensive care unit; Ref.: reference
Bold numbers denote statistical significance ($p < 0.05$)
* Evaluation of in-hospital all-cause mortality according to simplified PESI score was not adjusted as many of the covariates used for adjustments are already included in the simplified PESI

seem to be associated with an increased risk of in-hospital mortality in COVID patients.

In a previous analysis of the full PEPCOV cohort, COVID status was not associated with a higher risk of PE diagnosis in the ED[16]. The present study suggests that PE severity is different between COVID and non-COVID patients, with COVID patients presenting PE with a more distal topography, and less risk of RVD and a lower sPESI score. It is reported that the higher incidence of thromboembolism in COVID patient may be caused by hypercoagulability subsequent to an hyperinflammatory state[20]. These prothrombic abnormalities are associated with a higher risk of PE or disseminated intravascular coagulation, which is associated with a higher risk of mortality [21]. Autopsy studies reported that both macro- and microvascular thrombosis occurs frequently in COVID patients[22]. This may be in contrast with the physiopathology of PE in non-COVID patients, which are predominantly subsequent to DVT and may explain the difference in PE size in these two groups. Another plausible reason for the smaller size of PEs in COVID patients lies in the fact that other symptoms (many of which are not directly related to PE but to COVID itself) may lead patients to visit the ED and thereby be diagnosed with PE at an earlier stage. This would also explain at least partially that COVID patients present in the ED with PEs of lesser severity, with a lower percentage of RVD and a lower sPESI score.

Despite this milder severity, patients with COVID exhibited a higher in-hospital mortality for trivial reasons: COVID patients included in this study presented some symptoms of severity that led to ED visit and subsequent CTPA. The median age in this sample was 67 years, with a reported mortality in similar populations ranging from 10 to 20% in previous studies[23,24]. Nonetheless, there are scarce reports assessing risk factors for in-hospital mortality among COVID patients with PE. This study confirms what was described in non-COVID patients: higher sPESI scores and the presence of RVD are associated with a higher risk of mortality. Accordingly, the present findings suggest that the usual tools for PE risk stratification may be valid even in COVID patients[19,25,26]. Nonetheless, the poorer prognosis associated with RVD could be more related to acute changes in the pulmonary vascular system pressure resulting from the extensive lung parenchymal lesions caused by COVID itself rather than to circulatory obstructions by clots, which involve smaller arteries than in non-COVID patients. Interestingly, the size of the PE does not seem to have prognostic value in COVID patients: even with subsegmental PEs, 11 out of 56 (20%) of COVID patients died in the hospital. Since subsegmental PEs are usually associated with a very low risk of mortality, this suggests that COVID itself rather than PE largely drives the prognosis of patients with PE[27].

Finally, it is remarkable that the number of severity markers present in a particular patient, either COVID or non-COVID, was directly correlated with in-hospital mortality. However, while non-COVID patients with a low risk PE (non-lobar or larger PE, no RVD and sPESI=0) had a very low risk of mortality (0% in our series) as previously reported, this was not the case for COVID patients who had a substantial mortality risk (8.7% in our series) and warranted hospital admission and closer monitoring.

### *4.1. Limitations*

This study has some limitations. Firstly, the collection of data was retrospective, and it is likely that some data were not clearly reported in the medical notes, and therefore, might not have been properly collected in our database. This limitation, inherent to retrospective chart reviews, may be of limited extent because we mostly analyzed data that were reliably reported in medical charts, such as CTPA reports with characteristics of emboli. However, some items comprised in the sPESI score may not have been routinely collected and reported in the medical notes, particularly regarding past medical history. Another major limitation is the assessment of RVD that was only adjudicated in CTPA reports. The diagnostic performance of CTPA alone to diagnose RVD is unknown, and it is likely that the analysis of cardiac biomarkers and systematic echocardiography would have been more precise to detect the presence of RVD. Of note, the recent European guidelines recommend that PE severity be assessed depending on the numbers of markers of evidence of RVD, assessed with these three options[28]. The fact that only one was used to assess RVD in this study may explain the absence of association with in-hospital mortality in non-COVID patients with PE. An additional limitation is that there might have been a selection bias as described previously. Which patients underwent a CTPA for suspected PE was not uniform across the different EDs, and whether this represents

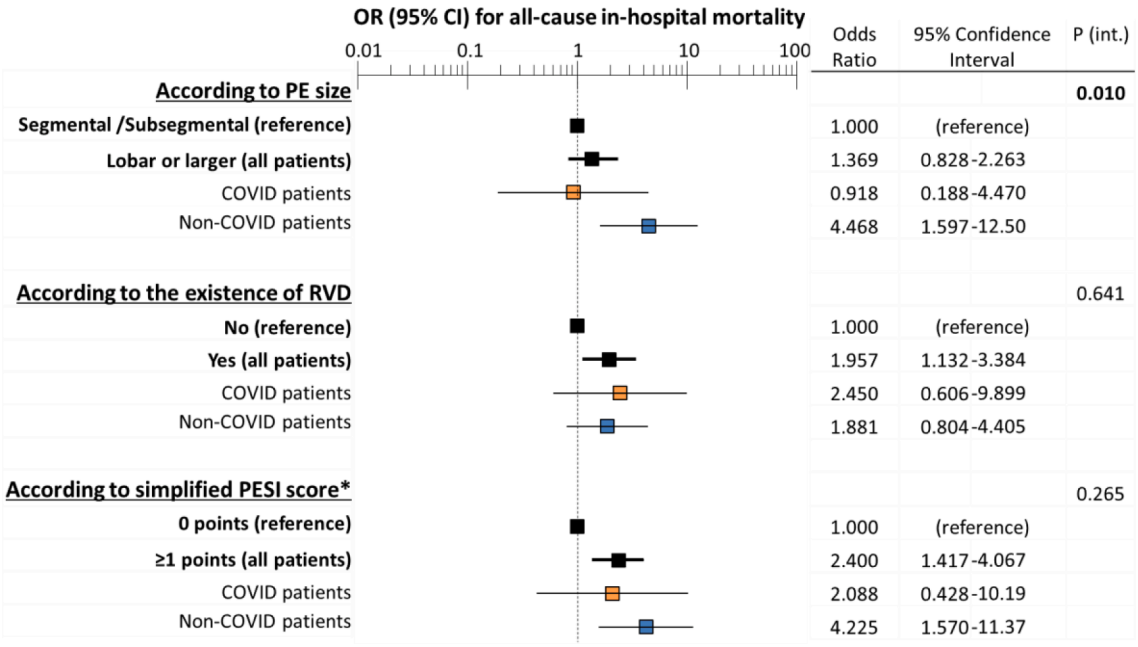


**Fig. 2.** Analysis of interaction of COVID status on the relationship between pulmonary embolism severity (assessed by pulmonary embolism size, existence of right ventricular dysfunction and simplified Pulmonary Embolism Severity Index [PESI] score) and adjusted in-hospital all-cause mortality.
*Evaluation of in-hospital all-cause mortality according to simplified PESI score was not adjusted as many of the covariates used for adjustments are already included in the simplified PESI
PE: pulmonary embolism; RVD: right ventricular dysfunction
Bold numbers denote statistical significance ($p < 0.05$).

**Table 4**
Comparison of in-hospital mortality in COVID and non-COVID patients according to the number of markers of pulmonary embolism severity (PE size lobar or larger, right ventricular dysfunction and sPESI score >0).

| | **Number of severity markers being present in patients with pulmonary embolism**(PE size lobar or larger; RVD; sPESI score >0) | | | | |
|---|---|---|---|---|---|
| | **None** | **One**(any marker) | **Two**(in any combination) | **Three**(all present) | *p* value(for trend) |
| **COVID patients (all clinically diagnosed)** | | | | | |
| Number of cases (%) | 92 (21.0) | 205 (46.7) | 109 (24.8) | 33 (7.5) | |
| Number of deaths (% of in-hospital mortality) | 8 (8.7) | 24 (11.7) | 16 (14.7) | 8 (24.2) | **0.024** |
| Odds ratio (95% confidence interval) | 1 (Ref.) | 1.39 (0.60–3.23) | 1.81 (0.74–4.44) | **3.36 (1.15–9.86)** | |
| **COVID patients (only PCR-confirmed)** | | | | | |
| Number of cases (%) | 65 (21.1) | 150 (48.7) | 72 (23.4) | 21 (6.8) | |
| Number of deaths (% of in-hospital mortality) | 8 (12.3) | 20 (13.3) | 12 (16.7) | 8 (38.1) | **0.020** |
| Odds ratio (95% confidence interval) | 1 (Ref.) | 1.10 (0.46–2.64) | 1.42 (0.54–3.74) | **4.39 (1.39–13.9)** | |
| **Non-COVID patients** | | | | | |
| Number of cases (%) | 85 (15.5) | 220 (40.1) | 184 (33.5) | 60 (10.9) | |
| Number of deaths (% of in-hospital mortality) | 0 (0) | 6 (2.7) | 16 (8.7) | 7 (11.7) | **<0.001** |
| Odds ratio (95% confidence interval)* | 1 (Ref.) | 5.18 (0.29–93.1) | 16.9 (0.99–282) | **24.0 (1.34–429)** | |
| **Subgroups comparison of in-hospital mortality between COVID and non-COVID patients** | | | | | |
| *p* value (using all clinically diagnosed COVID patients) | **0.007** | **<0.001** | 0.13 | 0.14 | - |
| *p* value (using only PCR-confirmed COVID patients) | **0.003** | **<0.001** | 0.11 | 0.11 | - |

PE: pulmonary embolism; RVD: right ventricular dysfunction; sPESI: simplified Pulmonary Embolism Severity Index
Bold numbers denote statistical significance ($p < 0.05$)
* Odds ratio and confidence interval was calculated using the approximation of Woolf. Since at least one value was zero, 0.5 was added to each value to make calculations possible.

the usual ED patient management is unknown, as patients were included during a very peculiar time (COVID outbreak). The 5% mortality rate of non-COVID patients with PE is consistent with what has previously been reported, suggesting that these results are likely valid in unselected ED patients with thromboembolism. Moreover, the present results only apply for PE diagnosed in the ED, and this is a very particular scenario, especially during the first pandemic wave[29,30]. Since then, some additional pandemic waves have passed and prevalence and/or severity

of PE could have changed, making our findings during the first wave not directly applicable to these successive waves. Therefore, readers should to be into account that COVID patients developing PE during hospitalization or in further pandemic waves could exhibit a different severity pattern with a different relationship with mortality. Finally, there was no size calculation and, accordingly, we could have committed a type-II error in some of our estimations.

### *4.2. Conclusion*

In this retrospective analysis of patients with PE diagnosed in the ED from two cohorts in Spain and France, patients with COVID exhibited PEs of less severity. However, COVID was associated with an increased risk of in-hospital mortality. This study suggests that the usual tools for risk stratification, specifically the sPESI and RVD, are still valid in COVID patients, while the size of a PE is not valid in this particular population infected by SARS-CoV-2.

## Declaration of Competing Interest

None.

## Appendix

The SIESTA network is formed by the following researchers and centers (all from Spain):

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