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Early View

Original article

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Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients

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Summary

We studied predictors of pulmonary embolism in severe COVID-19 and found that D-dimer level and lack of any anticoagulant therapy were associated with a 17-fold and 4-fold increase in PE respectively in COVID-19 patients with clinical signs of severity.

Abstract

Background: COVID-19 may predispose to venous thromboembolism. We determined factors independently associated with computed tomography pulmonary angiography (CTPA)-confirmed pulmonary embolism (PE) in hospitalized severe COVID-19 patients.

Methods: Among all (N=349) patients hospitalized for COVID-19 in a university hospital in a French region with a high rate of COVID-19, we analyzed patients who underwent CTPA for clinical signs of severe disease (SpO2 ≤ 93% or breathing rate ≥ 30/min); or rapid clinical worsening. Multivariable analysis was performed using Firth penalized maximum likelihood estimates.

Results: In total, 162 patients (46.4%) underwent CTPA (mean age 65.6±13.0; 67.3% males (95% confidence interval (CI) 59.5-75.5%)). PE was diagnosed in 44 patients (27.2%). Most PE were segmental and the rate of PE-related right ventricular dysfunction was 15.9%. By multivariable analysis, the only two significant predictors of CTPA-confirmed PE were D-dimer level and the lack of any anticoagulant therapy (odds ratio (OR) 4.0 (95%CI 2.4-6.7) per additional quartile, and OR 4.5 (95%CI 1.1-7.4) respectively). ROC curve analysis identified a D-dimer cut-off value of 2590 ng/mL to best predict occurrence of PE (AUC: 0.88, p<0.001, sensitivity 83.3%, specificity 83.8%). D-dimer level > 2590 ng/mL was associated with a 17-fold increase in the adjusted risk of PE.

Conclusion: Elevated D-dimers (>2590 ng/mL) and absence of anticoagulant therapy predict PE in hospitalized COVID-19 patients with clinical signs of severity. These data strengthen the evidence base in favour of systematic anticoagulation, and suggest wider use of D-dimer guided CTPA to screen for PE in acutely ill hospitalized patients with COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to venous thromboembolic (VTE) complications [1]. Preliminary reports suggest that the severe inflammatory response and other features of critical illness contribute to a procoagulant profile that predisposes to thrombotic events [2, 3]. Possible forms of coagulopathy include hemostatic abnormalities, notably with increased levels of D-dimers [2-5].

Incident pulmonary embolism (PE) has been reported in 20.6% to 30% of severe COVID-19 patients [6-10]. However, given the clinical presentation of patients with concomitant COVID-19 pneumonia, it is difficult to identify patients in whom PE should be suspected. In this regard, the indications for computed tomography pulmonary angiography (CTPA) remain to be defined.[11-14] Furthermore, the efficacy of VTE prophylaxis in patients with COVID-19 is poorly documented.[15]

In this context, this study aimed to: (1) determine the independent predictors of PE; and (2) evaluate whether anticoagulant therapy is effective for PE prevention in severe COVID-19 patients undergoing computed-tomography pulmonary angiography (CTPA) imaging.

Methods

Study design and population

Retrospective, single-centre study in a university tertiary care hospital in Besançon, France, with a high rate of COVID-19 [16]. We included all patients hospitalized from 15 March to 16 April 2020 with biologically proven COVID-19 pneumonia and CTPA performed due to clinical signs of severity, namely: $SpO2 \leq 93\%$ in room air, breathing rate of ≥ 30/min; or rapid clinical worsening [17]. Patients were followed until death or 5th May 2020, even if discharged before.

Laboratory confirmation of SARS-Cov-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs [18].

VTE prevention in COVID-19 patients comprised anticoagulant therapy at different doses, namely: prophylactic dose (low molecular weight heparin (LMWH): subcutaneous enoxaparin, 0.4 mg/kg once daily); or therapeutic dose, with either LMWH (subcutaneous enoxaparin, 1 mg/kg twice daily) or unfractionated heparin (UFH): 80 IU/kg bolus dose followed by 18 IU/kg per hour by continuous infusion to achieve an activated partial thromboplastin time ratio between 1.5 to 2.0; or oral anticoagulant. Management of COVID-19 was at the discretion of the physicians in charge.

In the context of the COVID-19 pandemic, the French national commission for the protection of personal data (CNIL) considers that, for single-centre observational research, the need for information of patients and families is waived. Our protocol followed the ethical guidelines of the declaration of Helsinki and was approved by our institutional review board. Results are reported in accordance with the STROBE guidelines.[19]

Data collection and variables recorded

Clinical and biological data

Baseline characteristics, in-hospital therapies, CTPA findings, and adverse events were recorded by research physicians in an anonymous case report form. For each patient, demographic data, medical history, and home treatments were collected prospectively at admission. Each patient had a blood sample drawn at admission, and then at least once daily thereafter.

Computed tomography protocol and imaging analysis

Multidetector CTPA was performed on a Revolution CT machine (GE Healthcare, Milwaukee, WI, USA) after intravenous injection of 60 ml iodinated contrast agent (Iomeprol 400 Mg I/mL, Bracco Imaging, Milan, IT) at a flow rate of 4 mL/s, triggered in the pulmonary trunk.

Imaging results were reviewed by two chest radiologists. Readers were blinded to clinical and biological features. Readers were asked to assess the COVID-19 pattern by quantitative visual CT evaluation, which consisted in grading acute COVID-19-related lung inflammatory lesions for each lobe, scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%), or 4 (76–100%), respectively. The total severity score was reached by summing the five lobe scores [20].

Readers were also asked to detect presence or absence on CTPA of PE, defined as a filling defect within pulmonary vessels [21]. When PE present, readers reported extent of PE; topography of PE; and signs of right ventricular (RV) dysfunction (i.e. enlargement of the pulmonary artery >35mm, abnormal position of the interventricular septum, right ventricular dilation (defined by a RV/left ventricular (LV) ratio >1 measured in the transverse or four-chamber view on CTPA [22]), or the presence of pulmonary infarction). In case of discordance between readers, scans were re-assessed to reach consensus.

Study objectives

The primary objective was to determine independent predictors of PE in COVID-19 patients with clinical signs of severity who underwent CTPA. The secondary objective was to evaluate whether anticoagulant therapy is effective for PE prevention in these patients.

Statistical analysis

Continuous variables are expressed as mean±standard deviation or median [Q1-Q3] as appropriate. Categorical variables are expressed as number (percentage). Unadjusted differences between

patients with and without CTPA-confirmed PE were compared using the chi square or Student t-test, as appropriate. To identify independent predictors of CTPA-confirmed PE in severe COVID-19 patients, we used Firth penalized maximum likelihood estimates to adjust our cohort study that includes a small sample size (n=162), to overcome the substantial bias linked to logistic regression [23].

Multivariable models included site of care (conventional ward vs ICU) as a random effect to account for patient clustering within departments. In multivariable models, continuous co-variates were categorized per quartile. All variables with a p-value<0.10 by univariate analysis were included in multivariable analysis. Linearity of significant co-variates in the multivariable model was verified before computing the Receiver Operating Characteristic (ROC) curve to determine the optimal cut-off value. The multivariable model was then repeated, including independent continuous variables dichotomized based on ROC curve results. The accuracy of the multivariable models was assessed by: (1) global model fit (Akaike Information Criteria and Bayes Information Criteria); (2) discrimination, using Harrell's C-statistic index; and calibration by visually plotting the mean of model-predicted CTPA-confirmed PE in each decile against observed PE.

All tests were two-sided. A p-value <0.05 was considered significant. Analyses were performed using SAS 9.4 (SAS institute Inc., Cary, NC).

Results

Study population

From 15 March to 16 April 2020, 349 patients were admitted to our tertiary care facility with a diagnosis of COVID-19. In total, 162/349 patients (46.4%) presented clinical signs of COVID-19-related severity, prompting the physician in charge to prescribe CTPA; 94 of these (58.0%) were in conventional wards and 68 (42.0%) in the intensive care unit (ICU); 48 (29.6%) were performed at admission, and 114 (70.4%) during the hospital stay. The 162 patients with CTPA imaging composed

the eligible study cohort. Overall, 44 (27.2%) had PE on CTPA, including 15 out of 94 (16.0%) in conventional wards, and 29 out of 68 patients (42.6%) in the ICU (Figure 1). Nine PEs (20.5%) were diagnosed at admission and 35 (79.6%) during the hospital stay (Supplementary Figure S1). The median time from hospital admission to CTPA was 5.0 days [0.0-8.3].

Table 1 summarizes the demographic and clinical characteristics of the population at admission. Mean age was 65.57±13 years, 67.3% (95%CI, 59.5-75.5) were male. The most common comorbidities were hypertension, dyslipidemia, obesity, diabetes mellitus, and a history of any heart disease. There were no significant differences between patients with vs without PE, except more men had PE. Factors known to be associated with an increased risk of VTE, such as history of VTE, cancer, and recent surgery did not differ between groups (Table 1).

There was no difference in home treatment between groups. Thirteen patients (8.0% (95%CI, 4.3-13.3)) were taking anticoagulant therapy at admission for a history of VTE or atrial fibrillation, (Table 1).

In total, during follow-up, 21 out of 162 patients died (13.0% (95% CI, 8.2-19.2)), 123 out of 162 were discharged alive (75.9% (95% CI, 68.6-82.3)), and the remaining 18 patients (11.1% (95% CI, 6.7-17.0)) were still in hospital and alive on May 5th, 2020. The mean duration follow-up of the 162 individuals was 38.0 days [33.8-42.3], corresponding to 6,156 person-days of COVID-19 exposure.

CTPA findings

CTPA findings are presented in Table 2. Twenty five out of 44 patients (56.8% (95%CI, 41.0-71.6)) had bilateral PE (Figure 2). Twenty-five patients (56.8% (95%CI, 41.0-71.6)) had segmental PE. The rate of RV dysfunction in the PE patient group was 15.9% (95%CI, 6.6-30.1).

Regarding the COVID-19-related CT pattern, half of the patients had more than 50% of affected lung parenchyma. There was an unadjusted difference in the extent of COVID-19-

related CT abnormality between patients with and without PE (p=0.001), whereby forms with >50% extension were predominantly found in patients with PE.

Biological parameters

Unadjusted comparisons of biological results from blood samples drawn on the day of CTPA are summarized in Table 3. The median D-dimer level was 4.1 times higher in the PE group compared to patients without PE (5364 ng/mL [2928-12275] vs 1310 ng/mL [800-2335], respectively). The rate of liver dysfunction, as assessed by alanine aminotransferase (ALAT), gamma glutamyl transferase (GT), and alkaline phosphatase values, was higher in those with PE versus those without. Cardiac troponin I levels were also higher in the PE group (0.018 µg/L [0.010-0.230] vs 0.010 µg/L [0.005-0.034], p = 0.003), whereas there was no difference in brain natriuretic peptide levels between groups. Arterial blood gas analysis revealed hypercapnia associated with elevated $HCO3^-$ in the PE group.

VTE prophylaxis during the hospital course

Overall, 141/162 patients (87.0% (95%CI, 80.8-91.8)) received anticoagulant therapy initiated at admission including 85.1% (95%CI, 78.1-90.5) with LMWH, 7.8% (95%CI, 4.0-13.5) with UFH, and 7.1% (95%CI, 3.5-12.7) with oral anticoagulant. Overall, 20.5% (95%CI, 9.8-35.4) of PE patients did not receive any anticoagulation therapy compared with 10.2% (95%CI, 5.4-17.1) of those without PE (unadjusted p = 0.083). The distribution of preventive and curative anticoagulant doses did not differ between groups: among those without PE, 68.8% (95%CI, 59.1-77.5) received a preventive dose, and 13.2% (95%CI, 7.4-21.2) received a curative dose, vs 85.7% (95%CI, 77.6-91.7) and 14.3% (95%CI, 8.3-22.4), respectively, among patients with PE (p = 0.535). The distribution of the different anticoagulant regimens is displayed in Figure 3.

Predictors of PE in severe COVID-19 patients.

By univariate analysis using the Firth's Penalized Likelihood estimator, male sex, D-dimer, $PaCO_2$, $HCO3^-$, blood urea, white blood cell count, extent of COVID 19-related CT scan abnormalities, alkaline phosphatase, gamma-GT, hospitalization in the ICU (vs conventional COVID ward) and any anticoagulant therapy were all significantly associated with PE diagnosis on CTPA (Supplementary Table 1).

By multivariable analysis, D-dimer level and the lack of any anticoagulant therapy were significantly associated with the occurrence of CTPA-confirmed PE (odds ratio (OR) 4.0 (95%CI 2.4-6.7) per additional quartile of D-dimers, and OR 4.5 (95%CI 1.1-7.4) respectively) (Figure 4).

Linearity was verified for D-dimers in the study population (test of linearity < 0.001). ROC curve analysis determined the optimal cut-off value of 2590 ng/mL for the D-dimer level to predict CTPA-confirmed PE in severe COVID-19 patients with high accuracy: AUC: 0.88, (95% CI, 0.809-0.932), p <0.001; Youden index 0.6708; sensitivity: 83.3 % (95% CI, 68.6-93.0), specificity : 83.8% (95% CI, 73.8-91.1), positive predictive value 72.9 % (95% CI, 61.7-81.8), and negative predictive value 90.5 % (95% CI, 82.9-95.0) (Figure 5).

Patients with D-dimers above the cut-off of 2590 ng/mL accounted for 36.0% (95% CI, 27.5-45.2) of the overall population, 42.6% (95% CI, 30.7-55.2) of patients in ICU, and 15.9% (95% CI, 9.2-24.9) of patients in conventional COVID wards. When analyzed in multivariable analysis as a binary variable, using the ROC-defined cut-off, a D-dimer level >2590 ng/mL was found to be a significant predictor of PE (OR 16.9, 95% CI, 6.3-45.0). The lack of any anticoagulation was also significantly associated with PE (OR 4.0, 95% CI 1.1-14.2) (Figure 4). The accuracy of both multivariable models was good, as assessed by global model fit, discrimination, and visual calibration, with predicted risks and their confidence intervals distributed around the observed risk of CT-scan confirmed PE (Figure 4) (Supplementary Figures S2 and S3).

Discussion

To the best of our knowledge, this study is the first to identify independent predictors of the occurrence of PE, from a cohort of 162 COVID-19 patients with clinical signs of severity. Our data show that PE was frequent in these patients, while elevated D-dimer levels and the absence of any anticoagulant therapy were both found to be independent predictors of PE. Specifically, a D-dimer level >2590 ng/mL was associated with a 17-fold increase, and lack of anticoagulation with a 4-fold increase in the risk of PE. Furthermore, the prevalence of PE remained high in this patient population, regardless of the type of anticoagulant strategy used. These data plead in favour of wider screening for PE by performing D-dimer guided CTPA in COVID-19 patients with signs of clinical severity.

The rate of PE observed in our study in hospitalized COVID-19 patients with clinical signs of severity is high (27.2%), and in line with rates reported in other studies. [6, 8-10]. The increased thrombo-embolic risk in COVID-19 patients could be enhanced by a procoagulant state generated by the severity of the infection,[2] the magnitude of the inflammatory response[3] and liver dysfunction [24-26]. The most frequently reported biological anomalies in COVID-19 patients include elevations of inflammatory markers such as CRP, D-dimers, ferritin and IL-6.[27, 28] In our population, D-dimer levels were four times higher in PE patients than in non-PE patients. This elevation of D-dimer levels has been established as being associated with severity of disease and mortality in COVID-19 patients and should be considered to reflect activation of the coagulation system in this setting.[3, 9, 28-30] In a Chinese study of 183 patients with COVID-19, D-dimer levels were 3.5 times higher in patients who died compared to patients who survived.[3] Similarly, COVID-19 patients with increased D-dimer concentration at admission (>1000 ng/mL) were reported to have an 18-times higher risk of in-hospital mortality than those with normal D-dimer levels.[28] Our data confirm this finding, and strengthen the evidence underpinning the

relation between elevated D-dimers and the risk of PE in COVID-19 patients.[1] The threshold for D-dimers that we identified, i.e. 2590 ng/mL, was the stronger independent predictor of PE in our population. To the best of our knowledge, this study is the first to identify a threshold for D-dimer levels that is an independent predictor of PE in COVID-19 patients after multivariable adjustment. Therefore, particular attention should be paid to search for potential PE in patients with clinical criteria of severity and with a D-dimer level above 2590 ng/mL, since PE is a life-threatening but potentially treatable condition [22].

Our data confirm that anticoagulation for the prevention of VTE is absolutely crucial in the most severe COVID-19 patients, and administration of anticoagulants reduces the risk of PE by 4. The relatively high proportion of patients who did not receive preventive anticoagulation in our study can likely be explained by the fact that 20.5% of patients had a diagnosis of PE at admission and were thus admitted directly from home with no anticoagulation in place. A recently published short report including 2773 COVID-19 patients showed that longer duration of anticoagulant treatment was associated with a reduced risk of in-hospital mortality (adjusted hazard ratio 0.86 per day, 95% CI 0.82-0.89).[31] In our study, regardless of the regimen used, the prevalence of PE remained high. However, our data do not enable us to determine the most appropriate prophylactic strategy, or to answer the question of whether curative doses are more effective than preventive doses in averting PE. This question was the subject of some debate during the development of a recent consensus on the prevention, antithrombotic therapy, and follow-up of thrombotic or thromboembolic disease in COVID-19 patients.[15] Indeed, in this document, the authors were unable to reach consensus on the optimal dosing of anticoagulant therapy, stipulating that “the majority of panel members consider prophylactic anticoagulation, although a minority consider intermediate-dose or therapeutic dose to be reasonable”.[15] There is thus a compelling need for prospective studies investigating the optimal dosing in patients with

severe COVID-19. In practice, pluridisciplinary discussion is warranted to evaluate the patient's hemorrhagic risk, and to weigh it against the risk of VTE. In light of our results, this point is of paramount importance in COVID-19 patients with severe forms of disease and evidence of activation of the coagulation system (e.g. elevated D-dimers) in whom prophylactic anticoagulant treatment appears to be essential for the prevention of PE. This is in accordance with a study of 449 patients with severe COVID-19 from China, where a reduction in mortality of around 20% was observed with heparin treatment in patients who had D-dimers exceeding 3000 ng/mL (6 times the upper limit of normal, ULN).[32] Furthermore, a recent expert panel document from the Global COVID-19 Thrombosis Collaborative Group postulates that LMWH and UFH may have anti-inflammatory and antiviral properties [33], although there is no established link between these properties and the course of COVID-19 disease.

Although current guidelines from professional societies of radiology recommend performing non-contrast chest CT to assess the COVID-19 pattern and its extension, [11-13] our data plead in favour of a wider screening strategy for PE by performing CTPA in COVID-19 patients who have signs of clinical severity and D-dimer levels > 2590 ng/mL. Indeed, the utility of CTPA over non-contrast CT is that it covers the whole spectrum of possible COVID-19-related complications, including COVID-19-related lung injuries, parenchymal bacterial infection, pleural effusion, pneumothorax, as well as enabling diagnosis of PE thanks to contrast injection. The high prevalence of PE in patients receiving anticoagulation is an additional argument in favour of this approach. The D-dimer cut-off identified in this study could be used to guide CTPA use, particularly in patients at risk of contrast-induced acute kidney injury. Indeed, it has recently been shown that acute kidney injury was associated with unfavourable outcome in hospitalized COVID-19 patients [34, 35]. Further prospective studies with larger sample sizes are warranted to externally validate the optimal D-dimer cut-off value related to PE in acutely ill hospitalized COVID-19 patients.

Our study has some limitations. Firstly, it is a retrospective study from a single-centre, and we cannot exclude the possible presence of unmeasured confounders. The sample size is relatively small, although it is nonetheless the largest series of COVID-19 patients undergoing CTPA reported to date. Only patients undergoing CTPA were included, and it is thus possible that the actual rate of PE was even higher than reported here. The selection of patients to undergo CTPA was based on clinical criteria of severity that may be debatable. Furthermore, most patients did not have compression ultrasonography screening during the study period. Our data do not make it possible to identify the most appropriate prophylactic anticoagulation strategy, and notably, do not provide answer the question of whether curative anticoagulation is more effective than preventive anticoagulation in averting PE. Finally, transthoracic echocardiographic data was not recorded in the present study to assess RV function in COVID-19-associated PE patients. However, current guidelines stipulate that CTPA is a validated alternative for the evaluation of RV dysfunction in acute PE [22].

Despite these limitations, this study is the first to identify independent predictors of PE, using robust statistical methods, and to report exhaustive biological and radiological findings as well as details of anticoagulant therapy in COVID-19 patients at the peak of the epidemic in France.

Conclusion

Pulmonary embolism is frequent in patients with clinically severe COVID-19 disease. Elevated D-dimer levels (>2590 ng/mL) and a lack of anticoagulation were found to be independent predictors of PE in these patients. These data strengthen the evidence base in favour of systematic anticoagulation, and suggest wider use of D-dimer guided CTPA to screen for PE in acutely ill hospitalized patients with COVID-19. The optimal dosing of anticoagulants remains unknown and warrants further prospective investigation.

Conflicts of interest

No author has any conflict of interest to declare.

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Figure Legends

Figure 1: Flowchart of the study population.

CTPA, computed tomography pulmonary angiography; ICU, intensive care unit; PE, pulmonary embolism

Figure 2: Computed tomography pulmonary angiography showing severe COVID-19 patter and bilateral pulmonary embolism.

Computed tomography pulmonary angiography of a 54 year old male with SARS-CoV-2 infection, 23 days after symptom onset and 17 days after admission to the Intensive Care Unit. Pulmonary CT angiography was performed because of severe hypoxemia despite invasive mechanical ventilation and showed, in addition to a severe COVID-19 CT pattern, bilateral acute pulmonary embolism of segmental location.

A. Pulmonary CT angiography, mediastinum window: Presence of acute PE as a filling defect inside the left superior lobe pulmonary artery, segmental - sub-segmental division of the lingula (red arrows)

B. Pulmonary CT angiography, parenchymal window: COVID-19 CT pattern with peripheral ground-glass opacities associated with areas of consolidation,

SARS-CoV-2: Severe Acute Respiratory Syndrome - CoronaVirus 2, COVID-19: Coronavirus 19, PE: Pulmonary Embolism.

Figure 3: Distribution of the different anticoagulant regimens in the whole study population and by group of patients with and without CTPA-confirmed pulmonary embolism.

Figure 4: Independent predictors of in-hospital CTPA-confirmed pulmonary embolism in severe COVID 19 patients, using the Firth's Penalized Likelihood estimator.

(A) Multivariable model including D-dimer analysed by quartile, D-dimer level (model fit: Akaike Information Criteria = 99.1 and Bayes Information Criteria = 133.1 for global model fit, and Harrell's C-statistic index = 0.91 for discrimination**.**

(B) Multivariable model including D-dimer as a binary variable defined by ROC curve analysis (model fit: Akaike Information Criteria = 104.6 and Bayes Information Criteria = 138.4 for global model fit, and Harrell's C-statistic index = 0.90 for discrimination).

Figure 5: Receiving Operating Characteristic curve identifying the cut-off value of D-dimer predictive of occurrence of pulmonary embolism.

AUC, area under the curve.

Table 1 : Baseline characteristics of the study population of COVID-19 patients who underwent computed tomography pulmonary angiography (N=162)

Variable	Whole population (N=162)	Patients without PE (N=118)	Patients with PE (N=44)	p-value
Age	65.57 (±13.00)	65.22 (±13.58)	66.52 (±11.41)	0.572
Males	109 (67.3% (95%CI, 59.5-75.5)	73 (61.9% (95%CI, 52.5-70.7)	36 (81.6% (95%CI, 67.0-91.7)	0.016
Obesity*	42 (25.9% (95%CI, 19.3-33.4)	28 (23.7% (95%CI, 16.4-32.4)	14 (31.8% (95%CI, 18.6-47.6)	0.296
Hypertension	80 (49.4% (95%CI, 41.5-57.4)	59 (50.0% (95%CI, 40.7-59.3)	21 (47.7% (95%CI, 32.4-63.3)	0.797
Diabetes mellitus	33 (20.4% (95%CI, 14.5-27.4)	25 (21.2% (95%CI, 14.2-29.7)	8 (18.2% (95%CI, 8.2-32.7)	0.427
Smokers	12 (7.4% (95%CI, 3.9-12.6)	9 (7.6% (95%CI, 3.5-14.0)	3 (6.8% (95%CI, 1.4-18.6)	0.581
Heart disease†	34 (21.0% (95%CI, 15.0-28.1)	26 (22.0% (95%CI, 14.9-30.6)	8 (18.2% (95%CI, 8.2-32.7)	0.382
History of heart failure	10 (6.2% (95%CI, 3.0-11.1)	8 (6.8% (95%CI, 3.0-13.0)	2 (4.5% (95%CI, 0.5-15.4)	0.458
History of VTE	13 (8.0% (95%CI, 4.3-13.3)	9 (7.6% (95%CI, 3.5-14.0)	4 (9.1% (95%CI, 2.5-21.7)	0.491
History of stroke	7 (4.3% (95%CI, 1.7-8.7)	7 (5.9% (95%CI, 2.4-11.8)	0 (0% (95%CI, 0.0-8.0)	0.103
COPD	11 (6.8% (95%CI, 3.5-11.8)	7 (5.9% (95%CI, 2.4-11.8)	4 (9.1% (95%CI, 2.5-21.7)	0.345
Respiratory	7 (4.3% (95%CI, 1.7-8.7)	5 (4.2% (95%CI, 1.4-9.6)	2 (4.5% (95%CI, 0.5-15.4)	0.612

insufficiency				
Chronic kidney disease	4 (2.5% (95%CI, 0.7-6.2)	2 (1.7% (95%CI, 0.2-6.0)	2 (4.5% (95%CI, 0.5-15.4)	0.298
Cancer‡	32 (19.8% (95%CI, 14.0-26.8)	25 (21.2% (95%CI, 14.2-29.7)	7 (15.9% (95%CI, 6.6-30.1)	0.304
Recent surgery§	3 (1.9% (95%CI, 0.4-5.4)	3 (2.5% (95%CI, 0.5-7.2)	0 (0% (95%CI, 0.0-8.0)	0.384
Usual Treatment				
Antiplatelet agents	38 (23.5% (95%CI, 17.2-30.8)	29 (24.6% (95%CI, 17.1-33.4)	9 (20.5% (95%CI, 9.8-35.4)	0.372
ACEI/ARB	62 (38.3% (95%CI, 30.8-46.3)	45 (38.1% (95%CI, 29.3-47.5)	17 (38.6% (95%CI, 24.3-54.5)	0.953
Betablockers	36 (22.2% (95%CI, 16.1-29.4)	26 (22.0% (95%CI, 14.9-30.6)	10 (22.7% (95%CI, 11.5-37.8)	0.925
Diuretics	22 (13.6% (95%CI, 8.7-19.9)	18 (15.3% (95%CI, 9.3-23.1)	4 (9.1% (95%CI, 2.5-21.7)	0.228
Anticoagulant	13 (8.0% (95%CI, 4.3-13.3)	10 (8.5% (95%CI, 4.2-15.1)	3 (6.8% (95%CI, 1.4-18.6)	0.509
Immunosupressants	9 (5.6% (95%CI, 2.6-10.3)	8 (6.8% (95%CI, 3.0-13.0)	1 (2.3% (95%CI, 0.1-12.1)	0.244

PE, pulmonary embolism; VTE, venous thrombo-embolism; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitors;

ARB, angiotensin-receptor blocker.

*Obesity defined as body mass index >30kg/m²

†Heart disease defined as any history of coronary artery disease, valvular heart disease, arrhythmia, dilated or hypertrophic cardiomyopathy

‡Cancer: active or prior

§Recent surgery defined as surgery within the previous 30 days.

Table 2: Findings on computed tomography pulmonary angiography in the study population (N=162)

Variable	Whole population (N=162)	Patients without PE (N=118)	Patients with PE (N=44)	p-value
Extent of COVID-19				
0 (0%)	13 (8.0% (95%CI, 4.3-13.3))	8 (6.8% (95%CI, 3.0-13.0))	5 (11.4% (95%CI, 3.8-24.6))	
1 (1-25%)	53 (32.7% (95%CI, 19.3-48.5))	43 (36.4% (95%CI, 27.7-45.8))	10 (22.7% (95%CI, 11.5-37.8))	
2 (25-50%)	48 (29.6% (95%CI, 22.7-37.3))	41 (34.7% (95%CI, 26.2-44.0))	7 (15.9% (95%CI, 6.6-30.1))	0.001
3 (50-75%)	33 (20.4% (95%CI, 14.5-27.4))	21 (17.8% (95%CI, 11.4-25.9))	12 (27.3% (95%CI, 15.0-42.8))	
4 (>75%)	15 (9.3% (95%CI, 2.6-21.9))	5 (4.2% (95%CI, 1.4-9.6))	10 (22.7% (95%CI, 11.5-37.8))	
Extent of emboli				
Bilateral			25 (56.8% (95%CI, 41.0-71.6))	
Topography of emboli				
Proximal			1 (2.3% (95%CI, 0.1-12.1))	
Lobar			16 (36.4% (95%CI, 22.4-52.3))	
Segmental			25 (56.8% (95%CI, 41.0-71.6))	

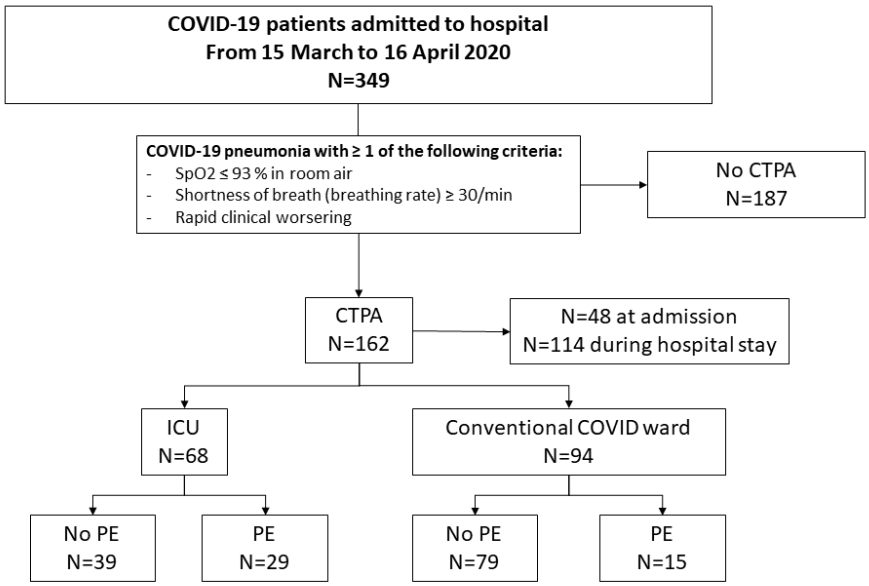
RV function				
RV/LV ratio >1			7 (15.9% (95%CI, 6.6-30.1)	

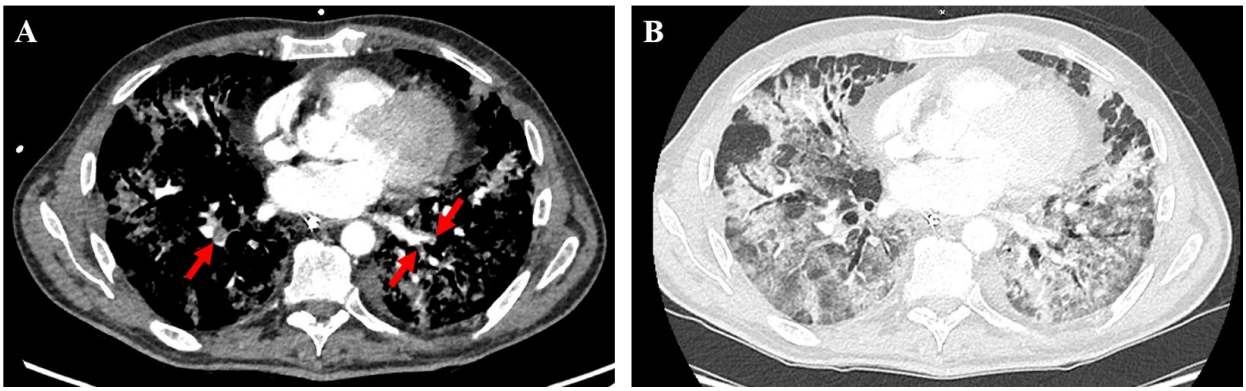
PE, pulmonary embolism; RV, right ventricle; LV, left ventricle; IV, interventricular.

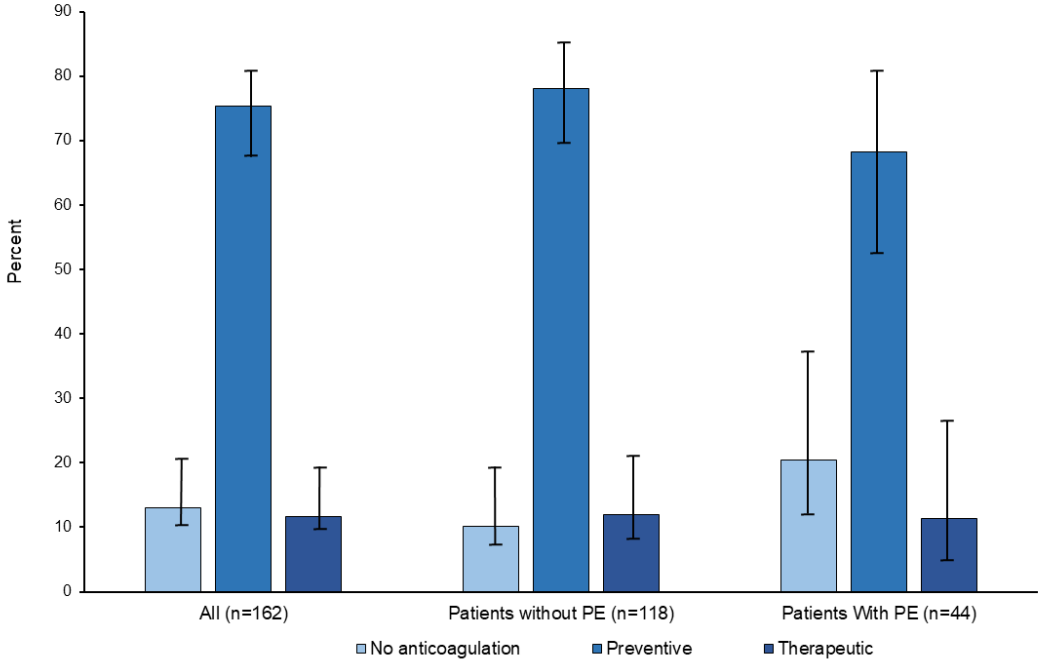
Table 3: Biological results from blood samples drawn at the time of computed tomography pulmonary angiography

Variable	N (n1/n2)	All	Patients without PE (n1)	Patients with PE (n2)	p-value
Hemostasis					
D-dimers, ng/mL	122 (80/42)	1920 (1068-4020)	1310 (800-2335)	5364 (2928-12275)	<0.001
Complete blood count					
Leucocytes, G/L	152 (112/40)	7.45 (5.80-10.20)	6.70 (5.53-9.48)	8.92 (6.55-13.85)	0.002
Lymphocytes, G/L	59 (49/10)	1.00 (±0.43)	0.94 (±0.42)	1.28 (±0.38)	0.023
Hemoglobin, g/dL	153 (113/40)	12.45 (±2.17)	12.65 (±2.11)	11.89 (±2.24)	0.056
Platelet count, G/L	153 (113/40)	266 (201.5-391)	246 (188-387)	343 (247-397)	0.006
Biochemistry					
Procalcitonin, ng/mL	102 (76/26)	0.23 (0.13-0.42)	0.26 (0.13-0.43)	0.17 (0.13-0.27)	0.130
Bicarbonates, mmol/L	159 (116/43)	24.00 (21.70-27.40)	23.55 (21.20-25.90)	26.60 (23.60-32.00)	<0.001
Urea, mmol/L	158 (115/43)	5.90 (4.48-9.43)	5.70 (4.20-7.90)	8.90 (5.10-13.50)	0.001

Creatininemia, µmol/L	157 (115/42)	71 (57-90)	72 (58-90)	70 (52-87)	0.754
ASAT, IU/L	135 (98/37)	46 (34-69)	44 (34-67)	53 (39-72)	0.194
ALAT, IU/L	147 (110/37)	37 (24-58)	36 (23-53)	54 (30-76)	0.010
Gamma Glutamyl Transferase, IU/L	130 (92/38)	91 (45-192)	79 (40-146)	160 (78-273)	0.002
Alkaline Phosphatase, IU/L	130 (92/38)	100 (68-160)	84 (66-135)	131 (82-248)	0.005
C-Reactive Protein, mg/L	158 (114/44)	115 (69-196)	114 (66-193)	121 (72-198)	0.861
Troponin Ic, µg/L	154 (111/43)	0.010 (0.010-0.040)	0.010 (0.005-0.034)	0.018 (0.010-0.230)	0.003
BNP, ng/mL	150 (112/38)	36 (12-104)	35 (12-91)	43 (13-189)	0.410
Blood gas					
pH	115 (76/39)	7.45 (7.40-7.49)	7.45 (7.40-7.49)	7.44 (7.40-7.49)	0.859
PaCO2, kPa	115 (76/39)	4.71 (4.24-6.81)	4.67 (4.18-5.62)	5.96 (4.45-7.44)	0.021
PaO2, kPa	115 (76/39)	10.20 (8.80-12.35)	9.95 (8.70-11.70)	10.60 (8.80-13.10)	0.268
Lactates, mmol/L	115 (76/39)	1.40 (1.20-1.70)	1.40 (1.20-1.70)	1.30 (1.10-1.60)	0.198

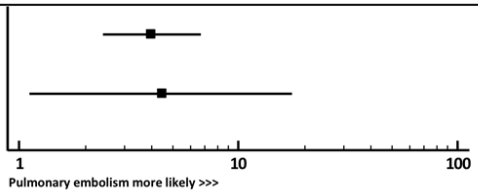

COVID-19 patients admitted to hospital
From 15 March to 16 April 2020
N=349
COVID-19 pneumonia with ≥ 1 of the following criteria:
- SpO2 ≤ 93 % in room air
- Shortness of breath (breathing rate) ≥ 30/min
- Rapid clinical worsering
No CTPA
N=187
CTPA
N=162
N=48 at admission
N=114 during hospital stay
ICU
N=68
Conventional COVID ward
N=94
No PE
N=39
PE
N=29
No PE
N=79
PE
N=15


A
B


90
80
70
60
50
40
30
20
10
0
Percent
All (n=162)
Patients without PE (n=118)
Patients With PE (n=44)
No anticoagulation
Preventive
Therapeutic

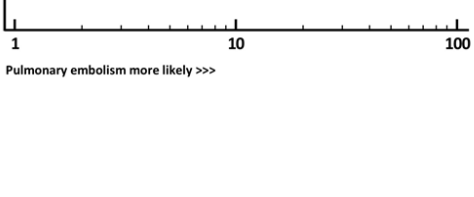
A

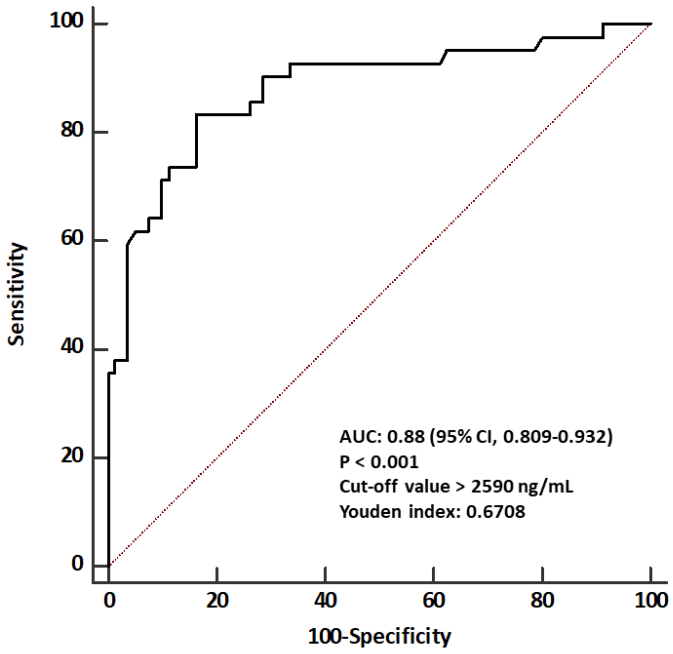
Characteristics	Relative rate of pulmonary embolism in severe COVID-19 patients	OR (95%CI)	χ^2	P-value
D-dimer (per quartile)		4.0 (2.4-6.7)	29.4	< 0.001
No anticoagulant therapy		4.5 (1.1-17.4)	4.7	0.03



B

Characteristics	Relative rate of pulmonary embolism in severe COVID-19 patients	OR (95%CI)	χ^2	P-value
D-dimer > 2590 ng/mL		16.9 (6.3-45.0)	32.1	< 0.001
No anticoagulant therapy		4.0 (1.1-14.2)	4.7	0.03




100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
100-Specificity
AUC: 0.88 (95% CI, 0.809-0.932)
P < 0.001
Cut-off value > 2590 ng/mL
Youden index: 0.6708

Supplementary material

Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients

Supplementary Table 1: Univariable predictors of in-hospital CTPA-confirmed pulmonary embolism in severe COVID 19 patients, using the Firth's Penalized Likelihood estimator

Variable	**Univariate analysis**	
	OR (95% CI)	**p-value**
Male sex	2.7 (1.1-6.1)	0.02
Extension CTPA findings	1.51(1.1-2.1)	0.03
White blood cell count (per quartile)	1.6 (1.1-2.1)	0.005
Blood urea (per quartile)	1.7 (1.2-2.4)	0.001
Gamma-GT (per quartile)	1.7 (1.2-2.3)	<0.001
Alkaline phosphatase (per quartile)	1.5 (1.1-2.1)	0.005
$PaCO_2$ (per quartile)	1.8 (1.3-2.5)	<0.001
$HCO3^-$ (per quartile)	1.7 (1.2-2.4)	0.001
No anticoagulant therapy	2.3 (0.9-5.9)	0.08
Conventional wards vs ICU	3.8 (1.8-7.9)	<0.001
D-dimer (per quartile)	4.7 (2.9-7.5)	<0.001
Model with D-dimer cut-off derived from ROC curve		
D-dimer > 2590 ng/mL	29.2 (11.6-73.2)	<0.001

CTPA: computed tomography pulmonary angiogram; Gamma-GT: Gamma-glutamyltranspeptidase; $HCO3^-$: bicarbonates; LMWH: low molecular weight heparin; ICU: intensive care unit.

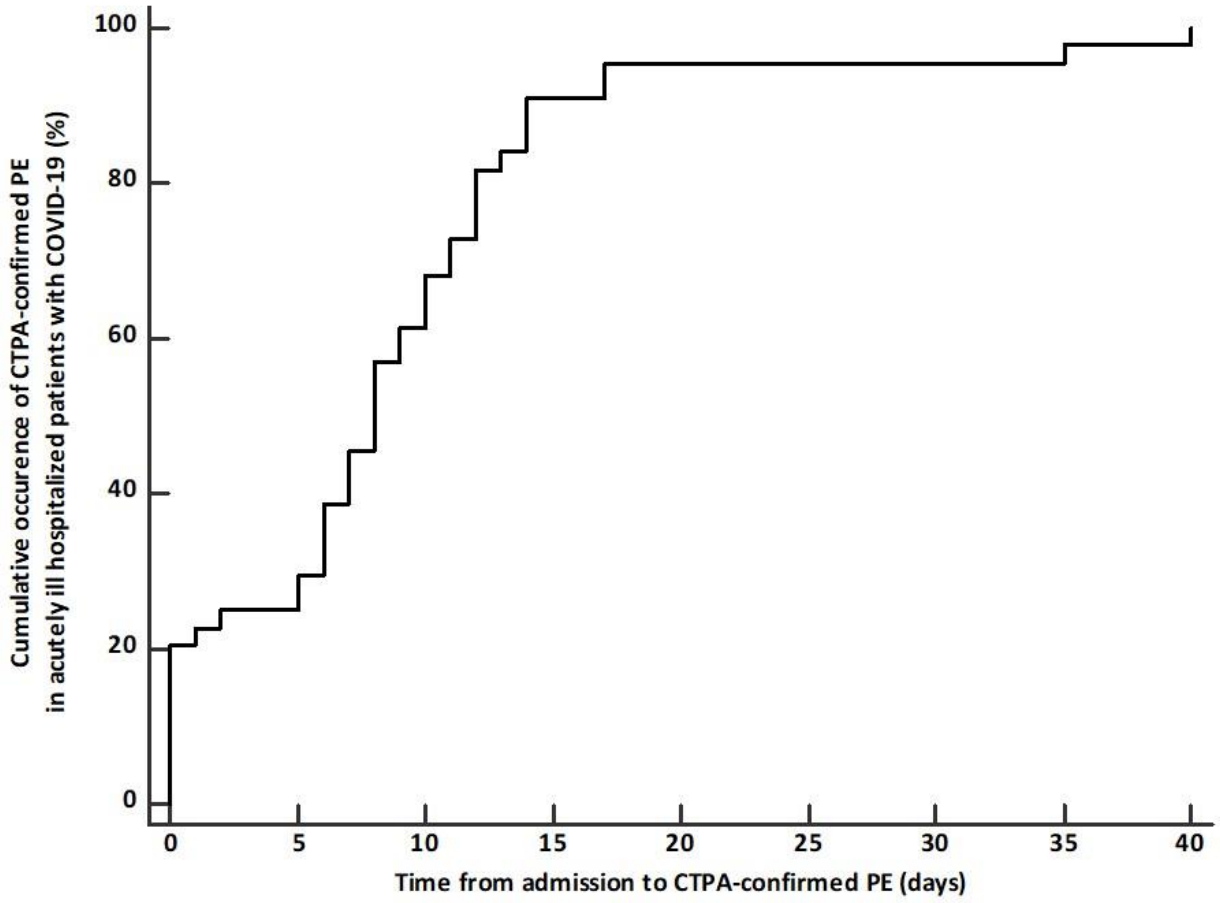


Figure S1: Cumulative occurrence of CTAP-confirmed pulmonary embolism between admission and CTPA in acutely ill hospitalized COVID-19 patients

COVID-19: coronavirus disease 2019; CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism

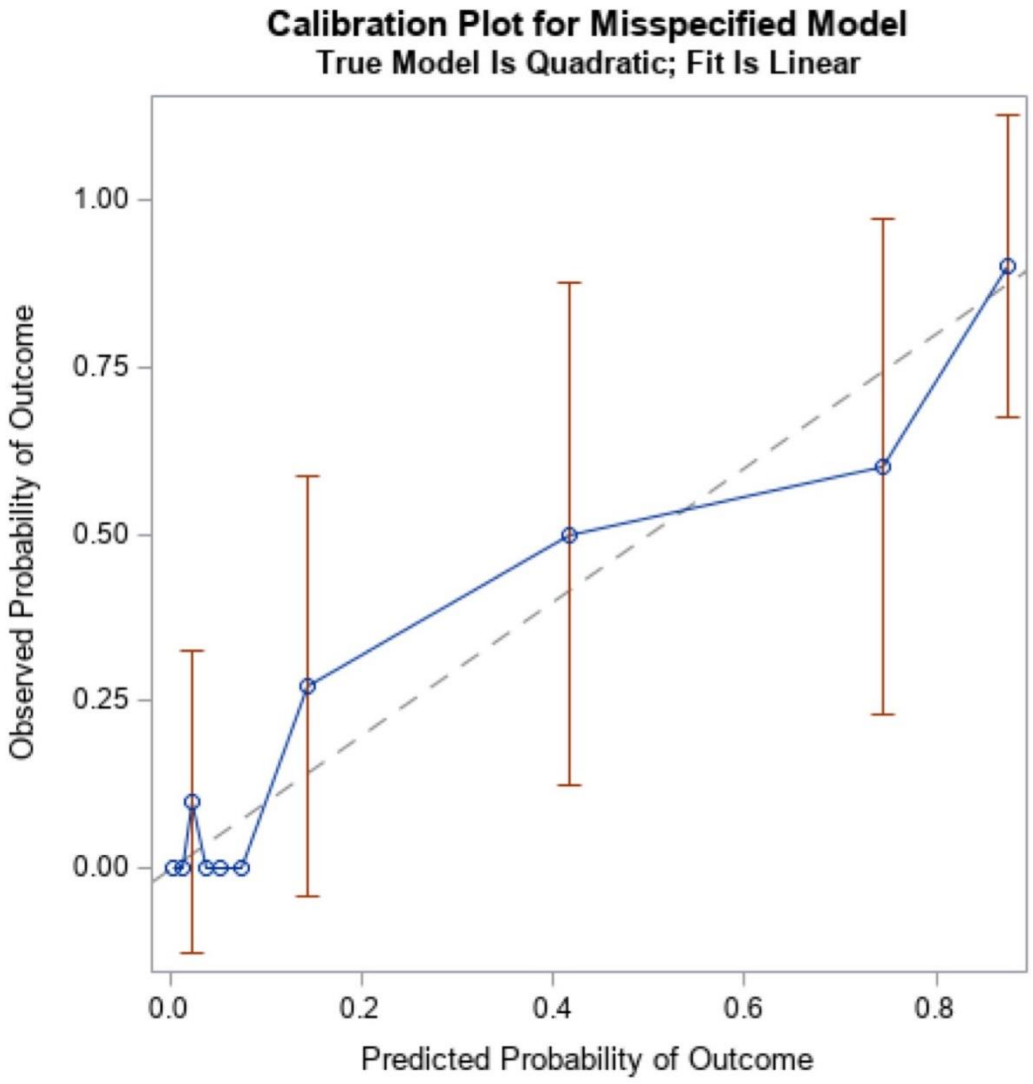


Figure S2: Decile calibration plots of the model predicting CTPA confirmed pulmonary embolism in severe Covid-19 patients. Model including D-dimer per quartile was well calibrated with the predicted risks and their confidence intervals distributed around the observed risk of pulmonary embolism. CTPA: computed tomography pulmonary angiography.

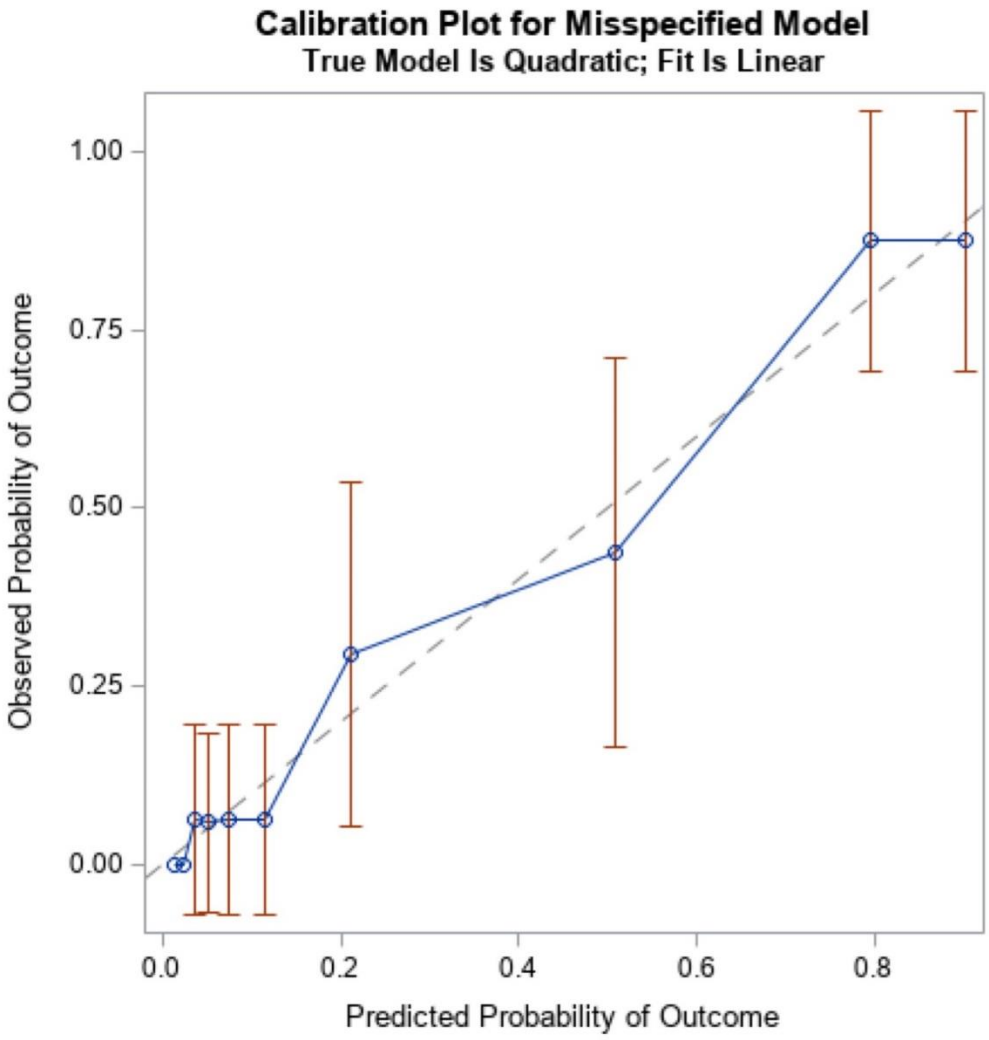


Figure S3: Decile calibration plots of the model predicting CTPA confirmed pulmonary embolism in severe Covid-19 patients. Model including the optimal ROC curve-derived cut-off value of D-dimer level (i.e. 2590 ng/mL) was well calibrated with the predicted risks and their confidence intervals distributed around the observed risk of pulmonary embolism. CTPA: computed tomography pulmonary angiography