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ORIGINAL ARTICLE

Clinical prediction model for pulmonary thrombosis diagnosis in hospitalized patients with SARS-CoV-2 infection

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ABSTRACT

Background and Aim: We aimed to develop a clinical prediction model for pulmonary thrombosis (PT) diagnosis in hospitalized COVID-19 patients.
Methods: Non-intensive care unit hospitalized COVID-19 patients who underwent a computed tomography pulmonary angiogram (CTPA) for suspected PT were included in the study. Demographic, clinical, analytical, and radiological variables as potential factors associated with the presence of PT were selected. Multivariable Cox regression analysis to develop a score for estimating the pre-test probability of PT was performed. The score was internally validated by bootstrap analysis.
Results: Among the 271 patients who underwent a CTPA, 132 patients (48.7%) had PT. Heart rate >100 bpm (OR = 4.63 [95% CI: 2.30–9.34]; $P < 0.001$), respiratory rate >22 bpm (OR = 5.21 [95% CI: 2.00–13.54]; $P < 0.001$), RALE score ≥4 (OR = 3.24 [95% CI: 1.66–6.32]; $P < 0.001$), C-reactive protein (CRP) >100 mg/L (OR = 2.10 [95% CI: 0.95–4.63]; $P = 0.067$), and D-dimer >3.000 ng/mL (OR = 6.86 [95% CI: 3.54–13.28]; $P < 0.001$) at the time of suspected PT were independent predictors of thrombosis. Using these variables, we constructed a nomogram (CRP, Heart rate, D-dimer, RALE score, and respiratory rate [CHEDDAR score]) for estimating the pre-test probability of PT. The score showed a high predictive accuracy (area under the receiver–operating characteristics curve = 0.877; 95% CI: 0.83−0.92). A score lower than 182 points on the nomogram confers a low probability for PT with a negative predictive value of 92%.
Conclusions: CHEDDAR score can be used to estimate the pre-test probability of PT in hospitalized COVID-19 patients outside the intensive care unit.
Relevance for Patients: Developing a new clinical prediction model for PT diagnosis in COVID-19 may help in the triage of patients, and limit unnecessary exposure to radiation and the risk of nephrotoxicity due to iodinated contrast.

1. Introduction

Since the beginning of the pandemic in December 2019, an increased risk of pulmonary thrombosis (PT) in patients with SARS-CoV-2 infection (COVID-19) has been reported, particularly in patients with severe disease, implying a worse prognosis [1-4]. A recent systematic review and meta-analysis that analyzed 36 studies involving 10.367

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COVID-19 patients found that the incidence of PT was 21% (95% CI: 18−24) [2].

PT characteristics in COVID-19 patients seem to differ compared to non-COVID-19 patients. As an example, lung thrombotic lesions in COVID-19 are frequently found in peripheral arteries [5] and the reported incidence of concomitant deep vein thrombosis is low [6]. These data may suggest that local thrombosis rather than embolism is the underlying pathophysiological mechanism in these patients. A pro-thrombotic state occurs in COVID-19; Endothelial dysfunction, complement activation, and pro-inflammatory cytokine release result in a dysregulation of the coagulation cascade with subsequent microclot generation [7]. In addition, microclots are accompanied by an exudative interstitial edema with a high protein content (including fibrinogen and fibrin) that fills the alveoli generating hyaline membranes [8]. Thrombosis related to such immune mechanisms has been defined as immunothrombosis. Computed tomography pulmonary angiography (CTPA) is considered the first-line diagnostic technique in patients with suspected pulmonary embolism (PE) with sensitivity and specificity values between 96 – 100% and 89 – 98%, respectively [9]. In addition, CTPA provides other useful imaging parameters in diagnosing PE, such as the right ventricle (RV)/left ventricle (LV) ratio >1, and the interventricular septal bowing to the LV. Per the CHEST guideline and expert panel report for COVID-19, patients with PT in the setting of SARS-CoV-2 infection are considered to have a provoking factor and anticoagulation therapy for at least 3 months is therefore indicated [10].

Diagnosing PT in SARS-CoV-2 infection is challenging as signs and symptoms of PT and COVID-19 overlap and D-dimer levels are often elevated in the absence of thrombosis in these patients [11]. This raises the question when to suspect PT in COVID-19 patients. Several studies have reported that clinical predictive models used in the general population to determine the pre-test probability of PE are not completely applicable to COVID-19 patients [12-15]. This has led to an increase in the number of CTPA performed [16]. This approach to PT diagnosis in COVID-19 patients increases the risk of nephrotoxicity due to iodinated contrast in addition to the radiation risks and the potential nosocomial transmission of SARS-CoV-2 infection to both patients and health-care professionals during patient transfer to the radiology department [17]. Finally, the cost of the technique should be considered. Therefore, new prediction rules specifically designed for this population are needed.

The aim of this study is to develop a new simple clinical prediction rule to improve the pretest probability estimation of PT in hospitalized COVID-19 patients.

2. Methods

2.1. Study design

We conducted a single-center observational analytical study based on a retrospective cohort, following the STROBE recommendations for observational studies [18]. The study was approved by the Ethics Committee (CEI) of the Hospital Universitario Clínico San Carlos (code 22/282-E) and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was waived because of the retrospective nature of the study and clinical data were anonymized.

2.2. Patients and study setting

Consecutive adult patients who were attended in medical wards or the emergency department due to COVID-19 at Hospital Infanta Leonor–Virgen de la Torre University Hospital were included in the study. SARS-CoV-2 infection was diagnosed by reverse transcription-polymerase chain reaction (RT-PCR) or antigen detection test. The study period was between the March 1, 2020, and the February 28, 2022. Patients who underwent a CTPA for suspected PT were located through the computerized registry of the radiology department. Patients requiring anticoagulant therapy due to other reasons before CTPA were excluded from the study. Demographic, clinical, analytical, and radiological variables at the time of suspected PT were collected from electronic medical records using a standardized form. The severity of the pneumonia was evaluated using the Radiographic Assessment of Lung Edema (RALE) score that provides information, both the grade of pulmonary inflammation and the severity of COVID-19 [19]. Chest X-ray patterns (reticular, ground-glass opacities and lung consolidations) were also registered. These variables were selected for their potential relation with the previously proposed pathophysiological mechanisms of PT in COVID-19 [20,21].

2.3. Pulmonary artery computed tomography protocol

At present, CTPA represents the gold standard for PT diagnosis. To achieve an adequate enhancement of the pulmonary trunk and its branches our routine protocol for CTPA was performed using the "bolus tracking technique," administrating 70 – 80 mL of iodinated contrast agent (Iohexol 300 mg/mL, Omnipaque® 300, GE) and a 100 mL saline chaser at a flow rate of 4 mL/s. During intravenous injection of contrast, sequential axial slices are acquired at a region of interest (ROI) set in the pulmonary artery and when a threshold of 100 HU enhancement is met, the scan initiates. Reformatted images with standard reconstruction algorithm (mediastinum and lung) are obtained with a slice-thickness of 0.75 mm. The study was considered optimal when the pulmonary arteries were opacified but not the aorta.

2.4. Statistical analysis and clinical prediction model development

In the descriptive analysis, qualitative variables were expressed as absolute and relative frequency distributions, while quantitative variables were expressed as median with interquartile range (IQR). χ^2-test or Fisher's test was used for comparisons between qualitative variables, and the Student's *t*-test or the non-parametric Mann–Whitney U-test for quantitative variables according to whether or not they conformed to a normal distribution, respectively. The associations between different variables and the presence of PT were estimated using odds ratios (OR) with their corresponding

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95% confidence interval (CI). A multivariate analysis was carried out using a logistic regression model (backward-stepwise) to determine the optimal independent variables associated with the presence of PT. Youden's J statistic (J = sensitivity + specificity − 1) was used to determine the optimal cutoff value for each independent variable. Using these variables, we developed a clinical prediction model (nomogram) for estimating the probability of PT in an individual hospitalized COVID-19 patient. Based on the reported prevalence of PT in non-intensive care unit (ICU) COVID-19 patients, the optimal cutoff value to rule out PT was calculated with the macro "Calculation of the area and drawing of the ROC curve (1999 8c) JM. Domenesch-Massons and A. Bonillo-Martín for SPSS". For this cutoff point, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated. Discrimination was quantified by the area under the receiver–operating characteristics curve (AUC). Model calibration was evaluated as a measure of agreement between observed risk and predicted risk stratified according to risk score using Hosmer–Lemeshow χ^2 statistic. We performed an internal validation procedure based on bootstrap cross-validation in the following way: A new sample of subjects was created by randomly drawing (with replacement) a 30% of subject of the original cohort and the PT rate was estimated in the new dataset (thus, although statistically very unlikely, it is theoretically possible that a new sample formed by 2.000 replication of the same subject could be created). $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software, version 24.0 (SPSS, IBM Corp, Armonk, NY, USA).

3. Results

3.1. Patients' characteristics

Two hundred and seventy-one consecutive patients (5.76%) with suspected PT who underwent a CTPA were included in the study. Among them, 132 (48.70%) PT were confirmed (Figure 1).

Demographic, clinical, analytical, and radiological characteristics of patients with and without PT are shown in Table 1. One hundred and fifty-four patients (51.5%) were male, and median age was 64 (±16) years. In the univariate analysis, statistically significant differences were found between patients with and without PT in age, history of hypertension and the presence of previous cerebrovascular disease, coronary artery disease, chronic heart failure, and previous autoimmune disease. Among typical risk factors for PT significant differences were found in obesity, recent immobilization, and estrogen therapy. In patients with PT, heart rate and respiratory rate were higher compared to non-PT patients. Among laboratory parameters, there were statistically significant differences in D-dimer, C-reactive protein (CRP), serum creatinine, lactate dehydrogenase, ferritin, and lactic acid. Pulmonary infiltrates were usually bilateral with a peripheral distribution. Ground-glass opacity, followed by ground-glass opacity plus consolidation or reticular pattern, and consolidation were the most frequent findings in CTPA lung window. The pulmonary lobes most commonly involved were the right lower lobe (85.7%) and left lower lobe (80.3%). In the PT group, the location of the thrombi was proximal (central or lobar) in 33.3% (44/132) of patients, and peripheral (segmental or subsegmental) in 66.7% (88/132) of patients (Figure 2). During hospitalization, patients received corticosteroids (73%), antibiotics (49.4%), anti-cytokine antibodies (44.6%), and antiviral drugs (28%). Almost all patients received pharmacological thromboprophylaxis. RALE score showed a statistically significant association with PT. 10 patients (7.7%) in PT group and 9 patients (6.5%) in non-PT group needed invasive mechanical ventilation. Nine patients (6.9%) in the PT group died compared to 1 patient (0.7%) in the non-PT-group. Length of stay was longer in patients with PT.

3.2. Risk model development

In multivariate cox regression analysis, heart rate >100 bpm (OR = 4.63 [95% CI: 2.30 – 9.34]; $P < 0.001$), respiratory rate >22 bpm (OR = 5.21 [95% CI: 2.00 – 13.54]; $P < 0.001$), RALE score ≥4 (OR = 3.24 [95% CI: 1.66 – 6.32]; $P < 0.001$), CRP >100 mg/L (OR = 2.10 [95% CI: 0.95 – 4.63]; $P = 0.067$), and D-dimer >3.000 ng/mL (OR = 6.86 [95% CI: 3.54 – 13.28]; $P < 0.001$) were independent predictors of PT (Table 2). The AUC of the model was 0.877 (95% CI: 0.83 − 0.92) (Figure 3), with a sensitivity of 68.8%, a specificity of 90.8%, a NPV of 74.7%, and PPV of 88.9% (Table 3). The calibration curve of the nomogram showed that the predicted probability of PT agreed well with the actual probability.

3.3. Model validation

Internal validation showed similar results (Table 4). The AUC was 0.867 (95% CI: 0.86 − 0.86) (Figure 3), with a sensitivity of 77.9%, a specificity of 78.9%, a NPV of 78.2%, and PPV of 78.4% (Table 3).

3.4. Nomogram

We developed a nomogram (CRP, HEart rate, D-Dimer, RALE score, and Respiratory rate [CHEDDAR score]) for estimating the probability of PT in a hospitalized COVID-19 patient (Figure 4). Based on a previously reported prevalence of PT of 20% in non-ICU COVID-19 patients [2], the presence of <182 points on the nomogram was associated with a NPV of 92% to rule out PT (Figure 5).

4. Discussion

This study proposes a simple clinical prediction model that may help clinicians to decide whether a CTPA should be performed in non-ICU hospitalized COVID-19 patients with suspected PT estimating the pretest probability. In our study, age, common comorbidities, and classic risk factors for venous thromboembolism including obesity, recent immobilization, and estrogen therapy were not independent factors associated with PT diagnosis. In our cohort, the independent predictors for PT were heart rate, respiratory rate, increased serum CRP and D-dimer levels, and the extent of lung parenchymal damage on chest radiography at the time of suspected PT. These variables were

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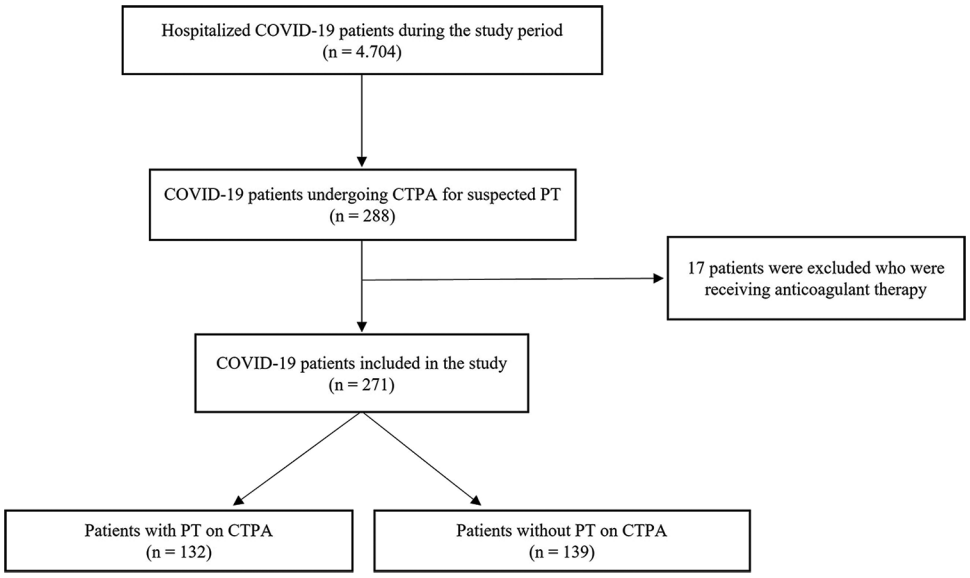

Figure 1. Flow chart of the study.
CTPA: Computed tomography pulmonary angiogram; PT: Pulmonary thrombosis

Table 1. Baseline characteristics of patients with and without PT

Variables	PT group (*n*=132)	Non-PT group (*n*=139)	*P*-value
Demographic characteristics			
Age–years (media [SD])	68.06 (±14.25)	61.69 (±17.21)	<0.001
Male–n (%)	69 (52.3)	85 (61.2)	0.661
Classic risk factors for PE–*n* (%)			
Previous venous thromboembolic events	2 (1.5)	1 (0.7)	0.531
Obesity (BMI >30 kg/m^2)	51 (38.6)	21 (15.1)	<0.001
Recent immobilization (last month)	7 (5.3)	0	0.021
Recent surgery (last month)	3 (2.3)	0	0.125
Thrombophilia	2 (1.5)	1 (0.7)	0.458
Estrogen therapy	5 (3.8)	0	0.006
Active cancer	19 (14.4)	11 (7.9)	0.089
Cardiovascular risk factors–*n* (%)			
Diabetes	28 (21.2)	30 (21.6)	0.941
Hypertension	76 (57.6)	61 (43.9)	0.024
Dyslipidemia	52 (39.4)	41 (29.5)	0.086
Smoking	14 (10.6)	12 (8.6)	0.581
Other comorbidities–*n* (%)			
Asthma	13 (9.8)	7 (5.0)	0.130
COPD	8 (6.1)	14 (10.1)	0.227
Cerebrovascular disease	10 (7.6)	2 (1.4)	0.014
Coronary artery disease	10 (7.6)	0	<0.001
Chronic kidney disease	7 (5.3)	7 (5.0)	0.921
Chronic heart failure	10 (7.6)	1 (0.7)	0.004
Chronic liver disease	6 (4.5)	5 (3.6)	0.693
Autoimmune disease	14 (10.6)	2 (1.4)	<0.001
Vital signs at PT the diagnosis			
Heart rate–bpm (media [SD])	103 (±20)	84 (±18)	<0.001
Respiratory rate–bpm (media [SD])	21 (±6)	16 (±2)	<0.001
Systolic blood pressure <90–mm Hg–*n* (%)	2 (1.5)	9 (6.4)	0.061

(Contd...)

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Table 1. *(Continued)*

Variables	PT group (*n*=132)	Non-PT group (*n*=139)	*P*-value
Median blood pressure–mm Hg (media [SD])	132 (±17.8)	128 (±16.9)	0.750
Fever (>37°C)–*n* (%)	67 (50.7)	63 (45.3)	0.531
O_2 saturation at admission (media [SD])	91 (±5)	92 (±6)	0.437
Laboratory findings at PT diagnosis			
Leukocytes–cells/mL (median [IQR])	8770 (6897 – 12007)	7600 (5500 – 10190)	0.130
Neutrophils–cells/mL (median [IQR])	6450 (4662 – 9425)	5350 (3500 – 7625)	0.158
Lymphocytes–cells/mL (median [IQR])	1100 (800 – 1600)	1200 (800 – 1950)	0.147
Platelets–cells/mL (median [IQR])	240.000 (177.000 – 305.000)	225.000 (165.000 – 305.000)	0.523
Haemoglobin–g/dL (median [IQR])	13.25 (12.10 – 14.40)	13.50 (12.40 – 14.73)	0.222
D-dimer–ng/mL [median [IQR])	5.620 (3.057 – 15.860)	1.635 (977 – 3.290)	<0.001
C-reactive protein–mg/L (median [IQR])	61.50 (12.75 – 124.80)	21.85 (5.03 – 65.40)	<0.001
Creatinine–mg/dL (median [IQR])	0.90 (0.74 – 1.13)	0.81 (0.64 – 1.00)	0.016
Serum albumin–g/dL (median [IQR])	3.0 (1.8 – 5.7)	3.2 (2.0 – 5.9)	0.320
Lactate dehydrogenase–UI/L (median [IQR])	267 (214 – 349)	219 (185 – 269)	<0.001
Ferritin–ng/mL (median [IQR])	525.50 (323.75 – 814.75)	351.00 (198.50 – 716.50)	0.025
Interleukin 6–pg/mL (median [IQR])	32.95 (9.73 – 98.18)	23.00 (5.65 – 55.10)	0.083
Lactic acid, mmol/L (median [IQR])	2.46 (1.87 – 3.50)	1.98 (1.58 – 2.78)	0.029
Troponin–ng/L (median [IQR])	0.03 (0.02 – 0.46)	0.02 (0.02 – 0.04)	0.138
RALE score (media [SD]) at PT diagnosis	5 (±3)	3 (±3)	<0.001
Treatment during hospitalization–*n* (%)			
Corticosteroids	96 (72.7)	102 (73.3)	0.780
Antiviral drugs	54 (40.9)	22 (15.8)	<0.001
Anti-cytokine antibodies	58 (43.9)	63 (45.3)	0.265
Antibiotic	86 (65.1)	48 (34.5)	<0.001
Thromboprophylaxis with heparin	128 (96.9)	139 (100)	0.587
Outcomes during hospitalization			
Transfer to ICU–*n* (%)	11 (8.5)	9 (6.5)	0.535
Need for mechanical ventilation–*n* (%)	10 (7.7)	9 (6.5)	0.697
In-hospital death–*n* (%)	9 (6.9)	1 (0.7)	0.007
Length of stay–days (median [IQR])	9.50 (6.00 – 20.25)	4.50 (1.00 – 12.25)	<0.001

SD: Standard deviation; PT: Pulmonary thrombosis; PE: Pulmonary embolism; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range; RALE: Radiographic assessment of lung edema; ICU: Intensive care unit

Table 2. Independent predictors for PT in multivariable cox regression analysis

Predictor variables	OR	95% CI	*P*-value
Heart rate>100 bpm	4.63	2.30 – 9.34	<0.001
Respiratory rate>22 bpm	5.21	2.00 – 13.54	<0.001
RALE score≥4	3.24	1.66 – 6.32	<0.001
C-reactive protein>100 mg/L	2.10	0.95 – 4.63	0.067
D-dimer>3.000 ng/mL	6.86	3.54 – 13.28	<0.001

OR: Odds ratio, CI: Confidence interval

used to construct an easy-to-use score that showed an excellent diagnostic accuracy and negative predictive value.

Several systematic reviews and meta-analyses have addressed the incidence of PT in COVID-19 patients with different results (ranging from 2% to 79%) [6,22-24]. In our study, the real incidence of PT is unknown because CTPA was performed based on clinical suspicion rather than systematic screening; therefore, the incidence might be underestimated, especially

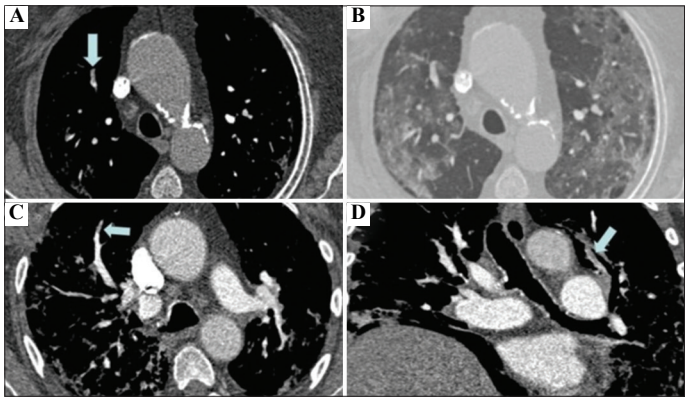

Figure 2. (A, C, D) show peripheral pulmonary thrombosis in two COVID-19 patients. Thrombi are present in segmental arteries in right upper lobe (A) and in segmental arteries of both lungs (C and D). In these two patients, there were also parenchymal abnormalities (ground glass opacities and septal thickening) better seen in CT lung window (B).

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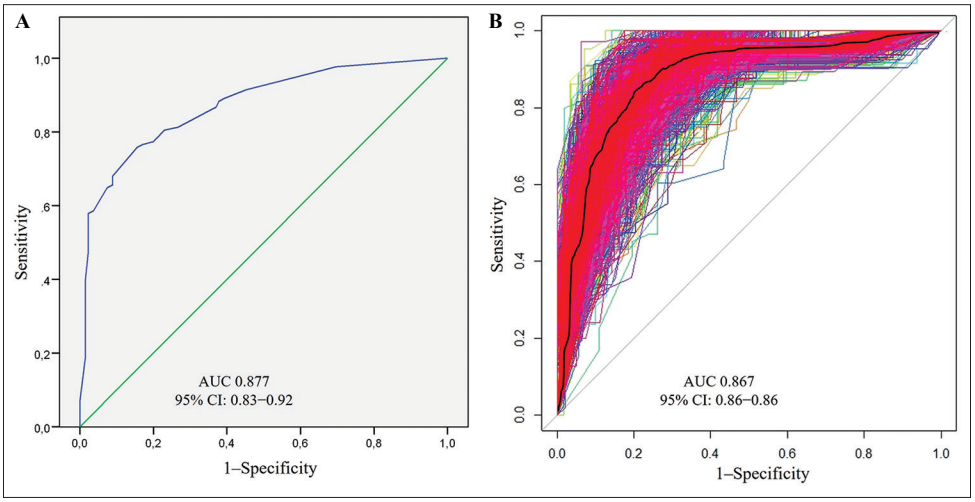

Figure 3. (A) The AUC according to the original nomogram. (B) The AUC according to the internal validation.

Table 3. Sensitivity, specificity, negative predictive value, positive predictive value, and the AUC for the original model and bootstrap analysis

Parameters	Original model	Bootstrap
AUC	0.877	0.867
Sensitivity	0.688	0.779
Specificity	0.908	0.789
Negative predictive value	0.747	0.782
Positive predictive value	0.889	0.784
Class Error	0.198	0.218

AUC: Area under the receiver–operating characteristics curve

Table 4. Bootstrap analysis

Predictor variables	OR	95% CI	*P*-value
Heart rate>100 bpm	4.92	2.09 – 11.86	0.002
Respiratory rate>22 bpm	5.84	1.86 – 22.42	0.012
RALE score≥4	3.42	1.52 – 7.93	0.011
C-reactive protein>100 mg/L	2.23	0.85 – 6.10	0.173
D-dimer>3.000 ng/mL	7.33	3.30 – 16.94	<0.001

OR: Odds ratio

in oligosymptomatic patients with segmental or subsegmental PT. Consequently, to determinate the best cutoff point to rule out PT in CHEDDAR score, the reported prevalence in a recent systematic review that involved the largest series of COVID-19 patients was used [2].

PE diagnosis guidelines recommend a standardized protocol using models to determine the pretest probability of PE [25]. The most frequently used models are the Geneva and the Wells score, the PERC rule, and the YEARS algorithm. The combination of a low or intermediate probability score and normal D-dimer level yield a NPV of 99%, and no further testing is required in these patients [26]. This diagnostic approach is particularly relevant in COVID-19 due to the risk of hospital SARS-CoV-2 transmission to other patients and healthcare professionals during patient's transfer to the radiology department

The most challenging aspect of PT diagnosis in COVID-19 patients is to establish when to perform a CTPA. Common symptoms of PE (fatigue, breathlessness, and chest pain) show a wide overlap with COVID-19 pneumonia, and D-dimer levels are often elevated in the absence of thrombosis [11,27]. Clinical and pathological observations have highlighted the role of endothelitis and the hyperinflammatory state in thrombosis physiopathology in SARS-CoV-2 infection [28]. Because the pathophysiological mechanism of PT in COVID-19, patients seems to be a local thromboinflammatory response rather than an embolization from a deep vein thrombosis, the scores that help to stratify the pretest probability of PE in non-COVID-19 patients have low accuracy in this clinical setting [12-15].

We found that vital signs were associated with PT. In line with the previous reports, heart rate was a risk marker of PT [29,30]. In a study conducted by Gil *et al.*, tachypnea >22 bpm was a predictive factor of PE in patients with COVID-19 [31]. We found an association between the extension of pneumonia and the presence of PT. The previous studies showed that patients with severe lung damage (>50%) evaluated on CTPA had a higher PE incidence rate [32-37]. D-dimer level was higher in patients with PE than in those without PE, and this has been confirmed in nearly every report on this topic [38-42]. D-dimer levels in COVID-19 patients in the absence of thrombosis may be elevated. Dehydration in critically ill patients causes tissue ischemia. This mechanism could be responsible for the elevated D-dimer serum levels, in COVID-19 patients [43]. Albumin is responsible for 80% of the oncotic pressure in the vessels. In a recent study, the albumin administration induced a decrease in D-dimer plasma levels, not because of the hemodilution, but because of the reduction of the ischemic complications [44]. Therefore, albumin infusion could be an "anticoagulant therapy" for critically ill patients with SARS-CoV-2 infection. In this clinical setting, lower specificity of D-dimer as a predictor of thrombotic events may be expected. Consequently, a higher cutoff value for diagnosis of PT in COVID-19 patients is proposed. In our study, as published previously [45,46], a cutoff of D-dimer

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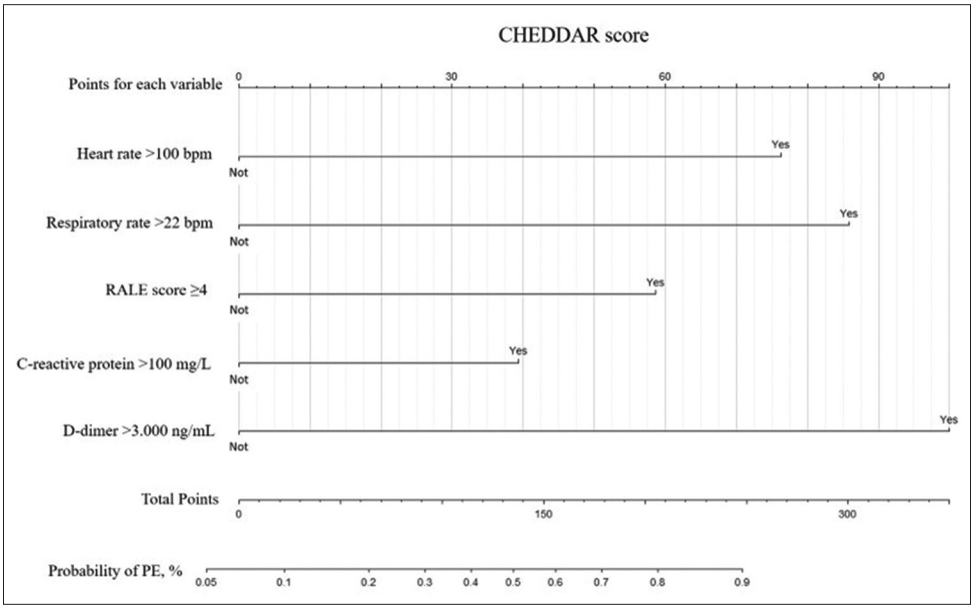

Figure 4. Nomogram to estimate the probability of PT in COVID-19 patients. Instructions: Draw a line upward to the points axis to determine the points for each predictor variables. Sum all the points from the variables and locate it on the "total points" axis. Draw a line down to the risk of PT axis to determine the patient's probability of PT (%). As an example, we suspect PT in a 77-year-old female with a heart rate of 116 bpm, a respiratory rate of 21 bpm, a RALE score of 5 and a CRP and D-dimer levels of 110 mg/L and 2.300 ng/mL, respectively. The points of each variable are 76 + 0 + 57.5 + 39 + 0 points; thus, the total score is 172.5 points.

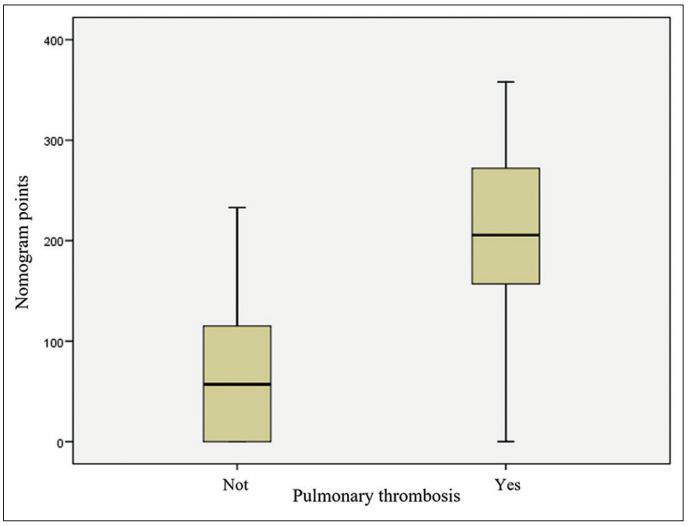

Figure 5. Box plot of nomogram points and pulmonary thrombosis.

level >3.000 ng/mL was associated with PT diagnosis. In addition, elevated CRP level was a predictor of PT occurrence in line with the previous reports [29,30]. All these factors are closely related to local excessive inflammatory response in COVID-19 patients.

We found a previous study that proposes a model to predict PE in COVID-19 patients, the CHOD score [29]. In this work, CRP, heart rate, oxygen saturation, and D-dimer levels were associated with higher rates of PE during hospitalization. Compared to our model, the best cutoff points for heart rate, CRP, and D-dimer were lower (≥90 bpm, ≥50 mg/L and ≥956 ng/mL, respectively). This score showed a high diagnostic accuracy (AUC 0.86; 95% CI: 0.8–0.93). CHOD score stratifies patients into three risk groups: low (0–2 points), moderate (3–5 points), and high risk (>5 points), with a PE rate of 4.5%, 36.8%, and 100%, respectively. Opposite to CHEDDAR score, the predictive variables for PE were collected at admission, and the model is only applicable to patients with elevated D-dimer levels, because patients with normal D-dimer were excluded from the study. This study was done during the first COVID-19 surge in Spain (from March 2020 to April 2020), whereas our study has been performed throughout different COVID-19 waves, including different SARS-CoV-2 variants, vaccinated population.

A novel finding of our study is the construction of a score to predict PT using five simple-to-measure variables (heart rate, respiratory rate, RALE score, CRP, and D-dimer) at the time of suspected PT. CHEDDAR score was constructed choosing the cutoff points with the best prognostic value for each variable. The diagnostic accuracy of the CHEDDAR score was remarkable. A CHEDDAR score below 182 points showed excellent ability to rule out PT with a NPV of 92%.

The main limitation of our study is its retrospective nature. The RALE score is subject to interobserver variability, although the degree of agreement between RALE score points and lung involvement on CTPA is high [47]. Finally, the model was constructed with COVID-19 patients and suspected PT who underwent a CTPA to obtain a certain diagnosis. Therefore, the model is applicable in this clinical scenario.

5. Conclusions

In our cohort CHEDDAR score at the time of suspected PT were independent predictors of PT. With these variables, we

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propose a simple clinical prediction model that helps to stratify the probability of PT in non-ICU COVID-19 patients. Our results need external validation before can be applied to clinical practice.

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Conflicts of Interest

The authors declared no conflicts of interest.

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Ethics Approval and Consent to Participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Ethics approval was obtained from the Hospital Universitario Clínico San Carlos (code 22/282-E). The need for informed consent was waived by the Ethics Committee of the Hospital Universitario Clínico San Carlos due to the retrospective nature of the study.

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