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The demographic, clinical, and medical manifestations of pulmonary thromboembolism development in COVID-19

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Background
Since the emergence of coronavirus disease 2019 (COVID-19), various clinical manifestations ranging from asymptomatic to severe, life-threatening courses have been presented. It is well known that COVID-19 patients are at an increased risk of pulmonary thromboembolism (PTE) development; however, the associated demographic, medical, and clinical factors for developing PTE remain unknown. The current study aimed to assess the characteristics of patients with PTE.

Methods
This case-control study was derived from an ongoing population-based investigation of hospitalized patients with COVID-19 pneumonia. The case group included 99 patients with PTE confirmed by computed tomography pulmonary angiography (CTPA), and the controls (N=132) were age-matched patients selected from the PTE-suspected patients with a negative CTPA. The demographic, medical, and clinical characteristics of the study population were entered into the study checklist and compared. A logistic regression test was used to determine the factors associated with PTE development.

Results
Among the 13,099 admitted patients, 690 (5.26%) were suspected of having PTE according to their clinical manifestations. CTPA was performed for suspected cases, and PTE was confirmed in 132 patients (19.13%). Logistic regression assessments revealed that male gender (OR, 2.39; 95%CI, 1.38–4.13), decreased oxygen saturation (OR, 2.33; 95%CI, 1.27–4.26), and lower hemoglobin (OR, 0.83, 0.95), and albumin (OR, 0.31; 95%CI, 0.18–0.53) levels were associated with PTE development.

Conclusion
PTE was confirmed in one-fifth of suspected patients who underwent CTPA imaging. Male sex, decreased oxygen saturation, and lower levels of hemoglobin and albumin were independent predictors of PTE in patients with COVID-19 pneumonia.

Key Words COVID-19, Pulmonary embolism, Computed tomography angiography, Coronavirus

INTRODUCTION

Since the emergence of coronavirus disease 2019 (COVID-19), various clinical manifestations ranging from asymptomatic disease to symptomatic presentations, including interstitial pneumonia, severe acute respiratory distress syndrome (ARDS), multi-organ failure, and death, have been reported [1]. The respiratory pattern of COVID-19 clinical evolution can be explained in three forms: mild symptomatic involve-

ment of the upper respiratory tract, non-life-threatening pneumonia, and severe pneumonia with ARDS, which initially presents as non-severe symptoms in the first 7–8 days and rapidly progresses until advanced respiratory support is required [2].

Numerous investigations in the literature have described a hypercoagulable state in patients infected with COVID-19, which leads to thromboembolic events, including pulmonary thromboembolism, coronary artery disease, arterial thrombosis, and ischemic strokes [3-5]. In addition, abnormal coagulation-related parameters have been frequently noted and are associated with a poor prognosis [6, 7].

The cytopathic reaction is one of the substantial theories regarding COVID-19 infection pathogenesis; however, from another point of view, the virus induces an unrelenting cascade of local cytokine release, inflammatory response, and a potentially detrimental immune reaction [8]. Excessive inflammatory response, in addition to hypoxia, immobilization, and diffuse intravascular coagulation in the setting of COVID-19 infection, contributes to the prothrombotic state [9].

Pulmonary thromboembolism (PTE) is one of the critical thrombotic conditions estimated to occur in 1.1–3.4% of COVID-19 patients, regardless of hospital admission. However, the data may have been influenced by the severity of the infection and the short-term follow-up of the patients. Additionally, there is an ongoing debate regarding the necessity for prophylactic and therapeutic anticoagulant use for patients with COVID-19. The current study aimed to assess the characteristics of patients with PTE to determine which COVID-19 patients are at an increased risk for PTE development and to provide subsequent anticoagulation therapy.

MATERIALS AND METHODS

Study population

This was a cross-sectional study of patients admitted to Amin and Alzahra Hospitals (affiliated with Isfahan University of Medical Sciences) due to COVID-19 pneumonia from May to June 2020. This case-control investigation was conducted on 231 patients suspected of PTE in two groups, including 99 patients with confirmed PTE according to computed tomography pulmonary angiography (CTPA) and 132 patients whose imaging was negative for PTE.

This study adhered to the tenets of the Declaration of Helsinki. The Institutional Ethical Committee at Isfahan University of Medical Sciences approved the study and all related protocols (IR.MUI.MED.REC.1399.692).

This was an observational study derived from an ongoing cohort study of a large population of COVID-19 pneumonia patients. Accordingly, the patients (or their legal guardian if needed) were informed about the protocols, reassured regarding the confidentiality of their personal information, and written informed consent was obtained from all participants before any intervention.

The study population was gathered from suspected PTE patients hospitalized due to COVID-19 pneumonia, which was confirmed by a positive polymerase chain reaction (PCR) test. Patients with pregnancy, immune deficiency, history of coagulopathies, and thromboembolic events within a month before hospitalization regardless of its type (deep vein thrombosis, pulmonary thromboembolism, cerebrovascular accidents, arterial thrombosis, or myocardial infarction), were excluded from the study. The included patients received anti-COVID-19 infection and anticoagulation therapy according to Iran's national guidelines [10].

Diagnosis of PTE

Patients with clinical manifestations suggestive of PTE (sudden dyspnea, pleuritic chest pain, hemoptysis, sudden hemodynamic instability, sudden general condition exacerbation, sudden loss of consciousness, and inconsistency of hypoxemia with the severity of lung involvement on computed tomography) were evaluated using D-dimer testing. CTPA was performed to confirm PTE in patients with elevated D-dimer levels [11].

Data collection

Demographic characteristics, including age, sex, smoking, comorbidities [diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), malignancy, cerebrovascular accident (CVA), ischemic heart disease (IHD), history of PTE], current smoking, and medical history (antiplatelet or anticoagulant administration prior to PTE assessments), were entered into the study checklist.

On admission, hemodynamic information [oxygen saturation (O_2 saturation), pulse rate, systolic and diastolic blood pressure, respiratory rate, and mobility] and laboratory assessments [complete blood count with differential (CBC diff), albumin, ferritin, C-reactive protein (CRP), D-dimer, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen, troponin, and lactate dehydrogenase (LDH)] were recorded in the study checklist. A reference laboratory performed all assessments to minimize potential bias.

CRP and LDH levels were measured every other day during hospital admission, while D-dimer levels were measured twice a week. The greatest difference between the on-admission measurements and the highest parameter level was calculated.

Patients with on-admission oxygen saturation below 90% and a respiratory rate above 30 breaths per minute were determined to have a severe course of COVID-19 pneumonia.

The patients who were given medications including hydroxychloroquine, antibiotics, remdesivir, interferon, favipiravir, corticosteroids, and kaletra prior to PTE diagnosis, were recruited as well.

Anticoagulation therapy administration status prior to PTE assessment was classified as no anticoagulant therapy, prophylactic, intermediate dose, or therapeutic dose. Anticoagulants were initiated before the incidence of thrombosis. Prophylactic doses included 5,000 IU subcutaneous unfractionated heparin (UFH) (three times a day) [for BMI

Table 1. Demographic, clinical, and laboratory characteristics of the studied population.

	No PTE (N=132)	PTE (N=99)	*P*
Age (yr), mean (SD)	58.0 (17.9)	59.0 (17.6)	0.665
Gender-male, N (%)	63 (47.7)	68 (68.7)	0.001[a]
Comorbidities, N (%)			
Diabetes mellitus	22 (16.7)	19 (19.2)	0.619
Chronic obstructive pulmonary disease	8 (6.1)	2 (2.0)	0.135
End-stage renal disease	0 (0)	3 (3.0)	-
Malignancy	3 (3.0)	3 (3.0)	1.000
Cerebrovascular accident	7 (5.3)	6 (6.1)	0.805
Ischemic heart disease	15 (11.4)	20 (20.2)	0.064
Previous history of pulmonary thromboembolism	1 (0.76)	1 (1.0)	0.838
Having the least of one comorbidity	48 (36.4)	38 (38.4)	0.753
Current smoking, N (%)	10 (7.6)	12 (12.1)	0.244
History of medications, N/N (%)			
None	31/103 (30.1)	66/94 (70.2)	<0.0001[a]
Aspirin	13/102 (12.8)	20/94 (21.3)	0.111
Clopidogrel	0/131 (0)	1/99 (1.0)	0.249
Anticoagulant prophylaxis	2/132 (1.52)	3/99 (3.0)	0.434
Therapeutic anticoagulant	0/132 (0)	2/99 (2.0)	0.156
On admission clinical presentations			
Systolic blood pressure, mean (SD)	127.1 (23.6)	124.1 (17.8)	0.297
Systolic blood pressure <90 mmHg, N (%)	3 (2.3)	1 (1.0)	0.637
Diastolic blood pressure, mean (SD)	77.8 (15.8)	78.8 (13.1)	0.624
Diastolic blood pressure <60 mmHg, N (%)	3 (2.3)	1 (1.0)	0.637
Pulse rate per minute, mean (SD)	92.3 (18.6)	94.7 (18.0)	0.332
Pulse rate >100 per minute, N (%)	33 (25.0)	33 (33.3)	0.165
Respiratory rate per minute-mean (SD)	24.5 (6.4)	24.6 (5.7)	0.838
Respiratory rate >30 per minute, N (%)	15 (11.4)	13 (13.1)	0.684
O_2 saturation (%), mean (SD)	86.1 (8.2)	81.8 (10.9)	0.001[a]
O_2 saturation t <90%, N (%)	83 (62.9)	79 (79.8)	0.005[a]
O_2 saturation 90–93%, N(%)	25 (18.9)	9 (9.1)	0.037[a]
O_2 saturation >93%, N(%)	24 (18.2)	11 (11.1)	0.138
Clinical presentations three days before CT-scan, N (%)			
Relative bed rest	75 (56.8)	34 (40.5)	0.019[a]
Complete bed rest	77 (58.3)	63 (75.0)	0.012[a]
On admission laboratory characteristics, mean (SD)			
Neutrophil count (per mL)	6,042 (4,100)	7,851 (4,016)	0.001[a]
Lymphocyte count (per mL)	1,239 (1,015)	1,048 (1,016)	0.161
Platelet $\times 10^3$ (per mL)	193.9 (95.7)	216.3 (94.4)	0.905
Neutrophil-to-lymphocyte ratio	6.9 (6.9)	10.3 (8.1)	0.001[a]
International normalized ratio	1.23 (0.56)	1.27 (0.43)	0.544
Hemoglobin (mg/dL)	13.3 (1.9)	12.6 (2.3)	0.006[a]
Ferritin (μg/L)	814.7 (582.5)	817.2 (554.7)	0.978
Fibrinogen degradation products (μg/mL)	25.8 (8.9)	26.2 (5.8)	0.871
Fibrinogen (mg/dL)	331.7 (111.4)	278.3(106.5)	0.040[a]
Prothrombin time (s)	13.8 (5.5)	14.1 (4.4)	0.721
Partial thromboplastin time (s)	37.2 (15.7)	32.4 (8.2)	0.010[a]
Albumin (g/dL)	3.64 (0.63)	3.25 (0.52)	<0.0001[a]
Troponin (ng/mL)	68.2 (232.8)	230.0 (495.1)	0.019[a]
D-dimer (μg/mL)	2,869 (3,285)	4,775 (3,641)	0.001[a]
C-reactive protein (mg/L)	67.6 (46.3)	85.2 (45.4)	0.006[a]
Lactate dehydrogenase (IU/L)	794.2 (385.1)	1,016.6 (527.4)	0.001[a]
Maximum laboratory characteristics-Median (IQR)			
D-dimer (μg/mL)	1,971 (817–4,732)	3,550 (2,259–8,191)	<0.0001[a]
C-reactive protein (mg/L)	77 (54–111)	98 (60–125)	0.034[a]
Lactate dehydrogenase (IU/L)	803 (629–1,215)	1,020 (683–1,380)	0.017[a]
Maximum increase compared to admission time, mean (min–max)			
D-dimer (μg/mL)	575.9 (0–8,909)	359.7 (0–9,363)	0.050
C-reactive protein (mg/L)	11.0 (0–102)	5.0 (0–86)	0.032[a]
Lactate dehydrogenase (IU/L)	188.6 (0–2,242)	114.3 (0–2,644)	0.206

[a]Chi^2/exact test for categorical variable, independent T-test or Wilcoxon rank-sum test for continuous variable were significant if *P*-value <0.05.
Abbreviation: PTE, pulmonary thromboembolism.

>40 kg/m^2: 7,500 IU subcutaneous UFH (three times a day)] or 40 mg subcutaneous enoxaparin (once daily) [for BMI >40 kg/m^2: 40 mg subcutaneous enoxaparin (twice daily)]. Intermediate doses included 7,500 IU subcutaneous UFH (three times a day) or 60 mg subcutaneous enoxaparin (daily). The therapeutic doses were determined as 80 IU/kg UFH bolus infusion, followed by 18 IU/kg/h UFH infusion, or 1 mg/kg subcutaneous enoxaparin (twice daily). The doses were defined according to national protocols [10]. Anticoagulant-related adverse effects, including gastrointestinal (GI) bleeding, hemoptysis, and hematuria, were recorded. Other probable side effects, such as easy bruising, petechiae, or purpura, were categorized as "other".

The latter outcomes were ICU admission requirement, discharge/death, and non-invasive ventilation (NIV)/ intubation.

Data analysis

The data were entered into the Statistical Package for Social Sciences (SPSS, version 22.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented as mean and standard deviation or median and range for the continuous variables, and frequency and percentages for categorical variables. The chi-square test or Fisher's exact test was used to compare categorical variables between the groups. Continuous variables were compared using the Mann–Whitney U test. Binary logistic regression analysis was applied to estimate the odds ratio and determine the association between the assessed factors and thrombotic events in the crude and adjusted models for age and sex. Statistical significance was set at $P<0.05$.

Table 2. Hospital-related characteristics of the studied population.

	No PTE	PTE	*P*
Prescribed Drugs	N=131	N=84	-
Hydroxychloroquine	61 (46.6)	20 (23.8)	0.001[a)]
Antibiotic	118 (9.1)	74 (88.1)	0.647
Remdesivir	23 (17.6)	14 (16.7)	0.866
Interferon	18 (13.8)	4 (4.8)	0.034[a)]
Favipiravir	2 (1.53)	1 (1.20)	0.845
Corticosteroid	87 (66.4)	68 (81.0)	0.020[a)]
Kaletra	13 (9.1)	7 (8.3)	0.695
Unknown	1 (0.75)	15 (15.1)	
Anticoagulation prior to PTE diagnosis, N (%)	N=130	N=84	-
None	34 (26.2)	38 (45.2)	0.004[a)]
Prophylactic doses	71 (54.6)	27 (32.1)	0.001[a)]
Intermediate doses	6 (4.6)	8 (9.5)	0.156
Therapeutic doses	19 (14.6)	11 (13.1)	0.754
Unknown	2 (1.5)	15 (15.1)	
Side effects of anticoagulants, N (%)	N=132	N=84	-
GI-bleeding	6 (4.6)	6/84 (7.2)	0.389
Hemoptysis	8 (6.1)	5/84 (6.0)	0.0001[a)]
Hematuria	2 (1.5)	3/84 (3.6)	0.327
Other	2 (1.5)	3/84 (3.6)	0.327
Missing	0 (0)	15 (15.1)	
Disease severity[a)], N (%)	13 (9.9)	10 (10.1)	0.949
Hospitalization outcome, N (%)	N=132	N=99	-
Intensive care unit admission	59 (44.7)	47 (47.5)	0.675
Non-invasive ventilation	12 (9.1)	25 (25.3)	0.001[a)]
Intubation	18 (13.6)	19 (19.2)	0.255
Discharge	124 (93.9)	81 (81.8)	0.004[a)]
Death	8 (6.1)	18 (18.2)	
Interval times-day, median (IQR)	N=132	N=99	-
Symptom to admission	7 (4–10)	7 (4–14)	0.467
Symptom to computed tomography, scan	13 (7–17)	14 (6–20)	0.841
Admission to computed tomography, scan	2 (0–7)	4 (3–8)	0.607
Admission to intensive care unit	2 (0–5)	3 (1–6)	0.247
Admission to discharged	9 (5–14)	10 (7–19)	0.033[a)]
Admission to dead	13 (12–21)	8 (13.5–30)	0.837

[a)]Chi^2/exact test for categorical variable, independent T-test or Wilcoxon rank-sum test for continuous variable were significant if *P*-value <0.05 and severity considered as O_2 sat <90 and respiratory rate >30.
Abbreviation: PTE, pulmonary thromboembolism.

RESULTS

Among the 13,099 patients admitted to the reference hospitals due to COVID-19 pneumonia, 690 (5.26%) were suspected of having PTE according to the clinical manifestations. CTPA was performed for suspected cases (N=690), among which PTE was confirmed in 132 patients (19.13%). Ninety-nine (75%) out of the 132 confirmed PTE patients had complete medical records. Eventually, they were randomly matched with 132 suspected PTE patients with negative CTPA reports.

The PTE patients were predominantly male, had poorer on-admission oxygen saturation levels, higher neutrophil-to-lymphocyte ratios (NLR), higher troponin, D-dimer, CRP, and LDH levels, and lower hemoglobin, fibrinogen, PTT, and albumin levels ($P<0.05$). Detailed information is presented in Table 1.

The hospital-related characteristics of the study population are shown in Table 2. According to this table, the two groups were remarkably different in terms of hydroxychloroquine, interferon, and corticosteroid use. The use of anticoagulants before PTE diagnosis, anticoagulant-related adverse effects, hospitalization outcomes, and the period between admission and discharge were the other parameters that were different between the two groups.

According to logistic regression, the requirement for NIV was significantly increased by PTE in both crude (OR, 3.37; 95% CI, 1.60–7.12) and adjusted models (OR, 3.40; 95% CI, 1.59–7.25); however, the other hospitalization outcomes were not associated with PTE incidence (Table 3).

Furthermore, corticosteroid administration was significantly associated with PTE development in crude (OR, 2.14; 95% CI, 1.11–4.13) and an adjusted model for severe COVID-19 (O_2 saturation <90 and respiratory rate >30) (OR, 2.17; 95% CI, 1.12–4.19).

Logistic regression analysis revealed that male sex and decreased O_2 saturation, hemoglobin, and albumin levels were independent predictors of PTE development as shown in Table 4.

DISCUSSION

The present investigation, which is a secondary study derived from an ongoing report of a large population of hospitalized patients with COVID-19 pneumonia, tried to assess the characteristics of patients with PTE due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. We found that male sex and lower oxygen saturation, hemoglobin, and albumin levels were independently associated with the risk of PTE development. Interestingly, corticosteroid administration led to an approximately 2.5-fold increased risk of PTE.

Respiratory tract infection is a well-known predisposing factor for PTE among hospitalized patients. Previous studies have shown that roughly 23–30% of COVID-19 patients were positive for PTE based on CTPA [12, 13], a statistic that is in line with the present study in which approximately 20% of the patients who underwent CTPA had PTE.

Searching the literature shows an increasing body of evidence regarding the increased risk of PTE due to COVID-19. This viral infection predisposes a person to venous thromboembolism due to the activation of a systemic inflammatory response, leading to an imbalance between procoagulant and anticoagulant effects [14].

Higher levels of biomarkers related to the hypercoagulable state induced by COVID-19, including fibrinogen, PTT, INR, and D-dimer, have been noted in our study, which is consistent with data from other studies conducted on PTE patients with COVID-19 pneumonia [4, 6]. Some studies have attempted to present a cut-off for D-dimer levels to distinguish PTE [15], although most of the recent guidelines did not favor routinely assessing this biomarker to diagnose venous thromboembolism [16]. Likewise, we did not detect D-dimer as a standalone predictor of PTE incidence among patients with SARS-CoV-2.

Male sex was accompanied by a 2-fold increased risk of PTE. Most previous studies have highlighted more severe lung involvement among men than among women [17, 18]. However, gender-based assessments of PTE due to COVID-19 are inadequate. In line with our study, Grillet and colleagues demonstrated that the male gender was a significant

Table 3. The effect of PTE on hospitalization outcomes.

		ICU admission	NIV	Intubation	Dead	Time from admission to	
						Discharge	Death
OR/exp(Beta)[a] (95% CI)	Crude	1.11 (0.66–1.88)	3.37 (1.60–7.12)[b]	1.50 (0.74–3.04)	3.44 (1.43–8.20)[b]	9.42 (0.36–245)	8.73 (0.002– 302)
	Adjusted[b]	1.09 (0.64–1.86)	3.40 (1.59–7.25)[b]	1.48 (0.73–3.02)	3.41 (1.41–8.28)[b]	4.25 (0.001–271.9)	9.86 (0.39–249.3)

[a]Binary logistic regression was used to estimate crude and adjusted odds ratio for categorical variables, and linear logistic regression was used to estimate crude and adjusted exponential beta for time to death and discharge. [b]Adjusted for severity, age, have at least one underlying disease. *P*-value <0.05.
Abbreviations: CI, confidence interval; ICU, intensive care unit; NIV, non-invasive ventilation; OR, odds ratio.

Table 4. Logistic regression analysis of factors associated with PTE.

	OR (95% CI)[c]	
	Crude	Adjusted[b]
Age	1.00 (0.98–1.01)	-
Gender-male	2.40 (1.39–4.14)[d]	2.39 (1.38–4.13)[d]
On admission clinical presentations		
O_2 saturation percentage	0.95 (0.92–0.98)[d]	-
O_2 saturation <93%	2.33 (1.27–4.26)[d]	-
Hemoglobin	0.83 (0.73–0.95)[d]	0.83 (0.73–0.95)[d]
Fibrinogen	0.99 (0.98–0.99)[d]	0.99 (0.99–1.00)
Albumin	0.32 (0.18–0.53)[d]	0.31 (0.18–0.55)[d]
NLR	1.07 (1.02–1.11)[d]	1.07 (1.02–1.12)
Troponin	1.00 (1.00–1.00)[d]	1.01 (1.00–1.01)[d]
D-dimer	1.00 (1.00–1.00)[d]	1.00 (1.00–1.00)[d]
CRP	1.00 (1.00–1.01)[d]	1.00 (1.00–1.01)[d]
LDH	1.00 (1.00–1.00)[d]	1.00 (1.00–1.00)[d]
Maximum laboratory characteristics		
D-dimer	1.00 (1.00–1.00)[d]	1.00 (1.00–1.00)[d]
CRP	1.01 (0.99–1.01)	1.01 (0.99–1.01)
LDH	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Maximum increase compared to admission time		
D-dimer	0.99 (0.99–1.00)	0.99 (0.99–1.00)
CRP	0.98 (0.96–0.99)[d]	0.98 (0.96–0.99)[d]
LDH	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Disease severity[a]	1.03 (0.43–2.5)	-
At least have one underlying disease	1.09 (0.63–1.86)	1.05 (0.61–1.85)
Hemoptysis	0.98 (0.30–3.10)	1.01 (0.30–3.34)

[a]Disease severity defined as O_2 sat<90, respiratory rate>30. [b]Adjusted by age and severity. [c]Binary logistic regression was used to estimate crude and adjusted odds ratio. [d]*P*-value <0.05.
Abbreviations: CRP, C reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil lymphocyte ratio.

risk factor for both PTE development and its severity [12]. Nevertheless, a cohort study by Cavagna *et al.* [19] was opposed. Generally, it is assumed that male sex hormones and the modulatory role of estrogen in immune response intensity and endothelial function are factors associated with a higher risk of complications in males. Similar logic has been noted for other conditions associated with inflammatory processes, such as atherosclerosis. On the other hand, males may consult physicians when in more deteriorated states than females. In addition, males usually have more predisposing factors, such as smoking or other comorbidities [17].

An on-admission oxygen saturation level of less than 93% was an independent predictor of PTE incidence associated with a 2.33-fold increased risk of PTE. Oxygenation status is a mainstay in the determination of COVID-19 severity, prognosis, and complications. Although PTE itself may lead to a V/Q mismatch, a decreased oxygen saturation level represents a more severe disease course that is accompanied by a storm of cytokine release, oxidative stress, and endothelial dysfunction, and therefore, an increased risk for thromboembolism [1, 20, 21].

Albumin is a well-known marker of health status in medicine. Accordingly, some researchers have tried to assess its value in predicting COVID-19 prognosis. In this regard, Li *et al.* [22] presented albumin as an independent predictor of mortality in critically ill patients, and Violi *et al.* [23] confirmed this theory in a general population of COVID-19 patients that was not limited to critically ill patients. In this study, we have shown up to a 20% decrease in the risk of PTE by each unit increase in albumin. Nevertheless, no data in this regard, a 4-fold increase in D-dimer levels among patients with hypoalbuminemia reinforces the theory about the association between decreased serum albumin level and hypercoagulable state [16]. Further investigations for the generalization of the data are required.

Hemoglobin was another hematological factor associated with PTE incidence due to COVID-19 pneumonia. Most studies reported insignificant differences between those with thromboembolic events and the control groups [24, 25]. Low levels of hemoglobin negatively affect blood viscosity, which in turn inhibits the function of anti-thrombotic mechanisms due to the reduction of stress formation on endothelial bed dysfunction [26, 27].

Most studies have unanimously described a poor prognosis of PTE in patients with COVID-19 [28, 29]. Surprisingly, we found that PTE independently did not affect any factor related to in-hospital outcomes, including ICU admission, intubation, discharge, and death, except for NIV requirement, which increased up to 3.5 times. Since the emergence

of COVID-19, NIV has been considered as a key intervention to preserve a patient's appropriate oxygenation and minimize the requirement for invasive strategies. On the other hand, it was assumed that patients under mechanical ventilation were predisposed to PTE development due to their more severe disease course [30]. Thus, the generalization of this outcome requires further investigation.

According to the findings of this study, PTE was confirmed in one-fifth of suspected patients who underwent CTPA imaging. Male sex, decreased oxygen saturation, and lower levels of hemoglobin and albumin were independent predictors of PTE in patients with COVID-19 pneumonia. Further investigations to provide an inexpensive, accessible, non-invasive, and safe scoring system to predict PTE development and initiate anticoagulation therapy for patients with COVID-19 are strongly recommended.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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