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Investigating the prevalence of and predictive and risk factors for pulmonary embolism in patients with COVID-19 in Nemazee Teaching Hospital

Mahnaz Yadollahi[1], Hessam Hosseinalipour[1], Mehrdad Karajizadeh[1], Muhammad Alinaqi[1], Pooria Fazeli[1], Mehrdad Jowkar[2], Kazem Jamali[1], Maryam Yadollahi[3]

[1]Trauma Research Center, Shahid Rajaee (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences, [2]Shiraz University of Medical Sciences, [3]Shiraz Central Hospital (MRI), Shiraz, Iran

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Correspondence to
Pooria Fazeli, M.sc.
Trauma Research Center, Shahid Rajaee (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences, Fars Province, Shiraz 71948-15711, Iran
E-mail: Pooriafazeli9270@gmail.com

Background
Pulmonary thromboembolism (PTE) is a significant contributing factor to vascular diseases. This study aimed to determine the prevalence of pulmonary thromboembolism and its predisposing factors in patients with COVID-19.

Methods
This cross-sectional study included 284 patients with COVID-19 who were admitted to Nemazee Teaching Hospital (Shiraz, Iran) between June and August 2021. All patients were diagnosed with COVID-19 by a physician based on clinical symptoms or positive polymerase chain reaction (PCR) test results. The collected data included demographic data and laboratory findings. Data were analyzed using the SPSS software. $P \leq 0.05$ was considered statistically significant.

Results
There was a significant difference in the mean age between the PTE group and non-PTE group ($P=0.037$). Moreover, the PTE group had a significantly higher prevalence of hypertension (36.7% vs. 21.8%, $P=0.019$), myocardial infarction (4.5% vs. 0%, $P=0.006$), and stroke (23.9% vs. 4.9%, $P=0.0001$). Direct bilirubin ($P=0.03$) and albumin ($P=0.04$) levels significantly differed between the PTE and non-PTE groups. Notably, there was a significant difference in the partial thromboplastin time ($P=0.04$) between the PTE and non-PTE groups. A regression analysis indicated that age (OR, 1.02; 95% CI, 1.00–1.004; $P=0.005$), blood pressure (OR, 2.07; 95% CI, 1.12–3.85; $P=0.02$), heart attack (OR, 1.02; 95% CI, 1.28–6.06; $P=0.009$), and albumin level (OR, 0.39; 95% CI, 0.16–0.97; $P=0.04$) were all independent predictors of PTE development.

Conclusion
Regression analysis revealed that age, blood pressure, heart attack, and albumin levels were independent predictors of PTE.

Key Words Thromboembolism, COVID-19, Mortality, Pulmonary risk factors

INTRODUCTION

The formation of blood clots in deep veins causes pulmonary thromboembolism (PTE), which is typically associated with asthma, heart attack, and pneumonia. It is an important risk factor for vascular diseases [1]. The annual occurrence rate of PTE is approximately 0.1% globally [1, 2]. Although anticoagulant therapy can help these patients to recover, if left untreated, it can be associated with a 30% in-hospital mortality rate. Furthermore, 8% of patients who receive treatment die, with a range of 2–50% [3]. In addition to vascular problems and high mortality, this disease imposes a huge financial burden on the healthcare system, with an estimated annual cost of one million dollars in the United States of America [4, 5]. The primary predisposing factors

for PTE are old age, underlying diseases, sedentary lifestyles such as smoking and inactivity, and elevated levels of D-dimer (>1 μg/mL) [2, 6-8]. The incidence rate of PTE in COVID-19 patients is reported to be 2.5% [9], and several studies have indicated its direct relationship with COVID-19 acute respiratory disease [10, 11]. The incidence rate of PTE in patients with COVID-19 is approximately 2.5%. COVID-19, with its mechanisms of excessive inflammation and activation of coagulation, can cause endothelial dysfunction and blood vessel clogging. It has also been reported that patients who died from COVID-19 had higher D-dimer levels than those who survived. Consequently, COVID-19 is considered a major risk factor for pulmonary embolism [2, 6, 12]. Examining a patient's clinical symptoms, along with diagnostic imaging and laboratory diagnostic tests (such as D-dimer), can be effective in the diagnosis of PTE [8, 13].

To date, only a few studies have been conducted to determine the prevalence and associated predisposing factors for PTE in COVID-19 patients in Iran. Therefore, this study aimed to investigate the prevalence of and predisposing factors for PTE in patients with COVID-19. Therefore, the findings of this study can aid in the early diagnosis of thromboembolism, prevention of disease complications, and reduction of mortality rates in patients with thromboembolism.

MATERIALS AND METHODS

This cross-sectional study included 284 patients with COVID-19 who were admitted to the Nemazee Teaching Hospital (Shiraz, Iran) between June and August 2021. During the study period, all participants who were diagnosed with COVID-19 by a physician based on clinical symptoms and imaging findings or by a positive polymerase chain reaction (PCR) test and who also had a diagnosis of pulmonary embolism were enrolled. All admitted patients with COVID-19 underwent chest non-contrast CT scans. Following the identification of patients with COVID-19 clinical symptoms and high D-dimer levels [14, 15], suspected patients underwent contrast-enhanced CT-scan imaging. The disease severity was classified using the CT severity score (CTSS), based on the percentage of lung lobar involvement reported by a radiologist, ranging from CTSS1 (≤5% lobar involvement) to CTSS5 (>75% lobar involvement) [16]. Patients experiencing symptoms of thromboembolism such as fever, chills, cough, sputum, shortness of breath, muscle pain, joint pain, sore throat, chest pain, diarrhea, vomiting, headache, dizziness, and limb numbness were also included. Patients with a history of allergic reactions to the iodine imaging

Table 1. Demographic information, clinical characteristics, and condition of the patients at the time of admission.

	Total (N=284)	PTE (N=62)	Non-PTE (N=222)	*P*
Age (yr), mean±SD	52.42±15.68	57.6±16.5	51±15.2	0.037
Sex (male)[a], N (%)	143	38 (61.3)	105 (51.2)	0.11
Pre-conditional health				
COVID-19 history, N (%)				0.999
Yes	68 (24)	13 (21.3)	45 (21.1)	
No	180 (63.4)	40 (65.6)	140 (65.7)	
Unknown	36 (12.6)	8 (13.1)	28 (13.1)	
Current smoking, N (%)	26 (9.1)	12 (19.3)	14 (6.3)	0.001
Malignancy, N (%)	27 (9.5)	2 (3.3)	25 (11.8)	0.052
Hypertension, N (%)	68 (24)	22 (36.7)	46 (21.8)	0.019
MI, N (%)	3 (1)	3 (4.5)	0 (0)	0.006
Diabetes, N (%)	40 (14)	12 (17.9)	28 (16.7)	0.81
CVA, N (%)	23 (8)	16 (23.9)	7 (4.9)	<0.0001
GI disease, N (%)	5 (1.7)	1 (1.5)	5 (2.4)	0.67
Allergy, N (%)	6 (2.1)	0 (0)	6 (2.8)	0.36
CRD, N (%)	5 (1.7)	2 (3.3)	3 (1.4)	0.33
DVT history, N (%)	8 (2.8)	4 (6.7)	4 (1.8)	0.1
On admission clinical presentation				
Temperature, °C (mean±SD)	36.89±0.58	36.8±0.63	36.9±0.57	0.44
RR, breaths per minute, (mean±SD)	21.41±4.09	21±2.17	21.5±4.5	0.68
HR, beats per minute, (mean±SD)	99.3±17.62	101.9±17.5	98.6±17.6	0.34
Systolic blood pressure, (mmHg)	122.47±27.19	125.2±22.2	121.6±26.7	0.35
Diastolic blood pressure, (mmHg)	89.13±24.62	87±21.2	89.8±25.6	0.87
Oxygen therapy				
Blood O_2 saturation, (mean±SD)	92.88±4.27	93.2±6.06	92.7±3.5	0.01

[a]Seven patients were missing.
Abbreviations: CRD, chronic respiratory disease; CVA, cerebrovascular accident; DVT, deep vein thrombosis; GI, gastrointestinal; HR, heart rate; MI, myocardial infarction; PTE, pulmonary thromboembolism; RR, respiratory rate.

material, those with incomplete records, and those without a diagnosis of thromboembolism were excluded from the study. All patients received prophylaxis and treatment for COVID-19 in accordance with the national guidelines developed in Iran [15]. A data collection form was designed to assess demographics, clinical, and laboratory data including age, sex; underlying diseases (diabetes mellitus, hypertension, heart diseases, and history of previous deep venous thrombosis); vaccination status; smoking; patient laboratory data (hemoglobin [Hb], prothrombin time [PT], international normalized ratio [INR], partial thromboplastin time [PTT], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], blood urine nitrogen [BUN], aspartate aminotransferase [AST], creatine phosphokinase [CPK], D-dimer, lymphocytes, alanine transaminase [ALT], neutrophils, creatinine, troponin); radiology and CT scan reports; clinical examinations; and treatment measures. Additional data collected included vital signs such as respiration rate, blood pressure, arterial oxygen saturation, heart rate; required respiratory facilities such as oxygen mask; multi-organ involvement; patients with ARDS; and patients with DVT history. Once PTE was diagnosed, color doppler sonography and other clinical assessments were performed to evaluate DVT. All collected data were extracted from patients' histories and physical examination sheets checked by an expert physician. The study protocol was approved by the Medical Ethics Committee of the Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1401.113).

Statistical analysis

The collected data were analyzed using the SPSS software version 21 (SPSS Inc., Chicago, IL, USA). Statistical analysis was performed using non-parametric tests, including the independent sample t-test, chi-square test, and logistic regression test. Descriptive data are reported as frequency (percentage), and analytical data are reported as mean±SD. In all analyses, the 95% confidence interval (CI) and two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

The current study included 284 patients with COVID-19 who were referred to the Nemazee Teaching Hospital (Shiraz, Iran) between June and August 2021 and whose diagnoses were confirmed either by a physician or a PCR test. Table 1 summarizes the demographic information, clinical features of the patients, and state of the study population at the time of admission.

A significant difference was observed in the mean age of individuals in the PTE and non-PTE groups (16.5±57.6 vs. 15.2±51.0, P=0.037). Likewise, out of a total of 284 pa-

Table 2. Laboratory findings in the PTE and the non-PTE populations of the study on admission.

On-admission laboratory tests (mean±SD)	Total (N=284) (mean±SD)	PTE (N=62) (mean±SD)	Non-PTE (N=222) (mean±SD)	*P*
Biochemistry parameters				
BUN (mg/dL)	19.71±17.24	21.2±15.5	19.2±17.8	0.2
Cr (mg/dL)	1.16±1.14	1.18±1.06	1.12±0.63	0.7
AST (IU/L)	46.65±28.9	58.4±33.8	43.2±26.4	0.01
ALT (IU/L)	45.1±36.2	41.8±31.1	53.4±45.8	0.1
ALKP (IU/L)	251.6±197.4	225.85±114.83	242±99.74	0.5
Total protein (g/dL)	6.7±0.78	6.14±0.81	5.84±0.64	0.1
Total bilirubin (mg/dL)	1.4±1.27	1.9±1.09	1.73±1.49	0.1
Direct bilirubin (mg/dL)	0.85±0.5	0.88±0.72	0.84±0.44	0.03
Albumin (g/dL)	3.2±0.49	3.11±0.51	3.3±0.47	0.04
CPK (IU/L)	149.5±158.8	150.2±161.65	152.2±153.7	0.9
LDH (IU/L)	1,080.0±1,058.4	1,072.3±1,017	1,284±1,023	0.2
Troponin (ng/mL)	85.4±114.7	41.4±60.7	173.4±149.4	0.05
Hematologic parameters				
Hemoglobin (mg/dL)	12.46±2.46	12.32±2.48	12.98±2.35	0.08
ESR (mm/h)	32.8±25.08	32.7±22.4	35.5±37.1	0.8
PLT×10^3 (per mL)	226±105.25	209.9±98.3	230.9±107.7	0.2
PT (s)	15.9±4.14	15.47±3.31	16.96±5.66	0.1
PTT (s)	34.3±16.8	35.0±18.7	31.2±5.64	0.04
INR	1.19±0.32	1.16±0.26	1.28±0.45	0.1
Serologic and immunologic parameters				
CRP (mg/L)	74.27±70.07	81.7±68.5	73.6±71.1	0.4
D-dimer (μg/mL)	3,020.5±2,961.4	2,048.4±1,824.4	4,575.9±3,946	0.2

Abbreviations: ALKP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; LDH, lactate dehydrogenase; PLT, platelet; PT, prothrombin time; PTE, pulmonary thromboembolism; PTT, partial thromboplastin time.

tients, 62 patients were diagnosed with PTE, 38 (61.3%) of whom were males. There were 105 (48.8%) males among 222 non-PTE patients, and there was no statistically significant difference between the two groups (P=0.11).

Smoking was significantly more prevalent in the PTE group than in the non-PTE group (19.3% vs. 6.3%, P=0.001). Moreover, the PTE group had a significantly higher incidence of hypertension (36.7% vs. 21.8%, P=0.019), myocardial infarction (4.5% vs. 0%, P=0.006), and stroke (23.9% vs. 4.9%, P<0.0001) than the non-PTE group. With regard to the condition of the patient on arrival, the level of blood oxygen saturation in the PTE group was significantly higher than that in the non-PTE group (93.2±6.06 vs. 92.7±3.5, P=0.01). The patients' clinical symptoms such as fever, chills, cough, sputum, shortness of breath, muscle pain, joint pain, sore throat, chest pain, diarrhea, vomiting, headache, dizziness, and limb numbness were also assessed in these two groups, and no significant differences were observed (P>0.05). For each examined CT scan parameter (ground-glass appearance, diagnosis of COVID-19, lymphadenopathy, pleural effusion, hemothorax, pneumothorax, pulmonary fibrosis, pericardial effusion, lung cavity, atelectasis, and pneumomediastinum), there was no significant difference between the PTE and non-PTE groups (P>0.05). Laboratory findings on admission in the PTE and non-PTE groups are presented in Table 2.

Direct bilirubin levels (0.88±0.72 vs. 0.84±0.44, P=0.03) and albumin levels (3.11±0.51 vs. 3.3±0.47, P=0.04) differed significantly between the PTE and non-PTE groups. According to hematological results, there was a significant difference between the PTT levels in the PTE and non-PTE groups (35.0±18.7 vs. 31.2±5.64, P=0.04). Other biochemical, hematological, and serological data did not differ significantly between the two groups (P>0.05). Besides, regression analysis showed that age (OR, 1.02; 95% CI, 1.00–1.004; P=0.005), blood pressure (OR, 2.07; 95% CI, 1.12–3.85; P=0.02), heart attack (OR, 1.02; 95% CI, 1.28–6.06; P=0.009), and albumin level (OR, 0.39; 95% CI, 0.16–0.97; P=0.04) were independent predictive factors of PTE development (Table 3). The multivariate logistic regression analyses of PTE risk factors indicated that age (OR, 1.02; 95% CI, 0.99–1.05; P=0.12) and albumin level (OR, 0.35; 95% CI, 0.13–0.92; P=0.03) were associated with the development of PTE (Table 4).

Table 3. The logistic regression analysis of PTE predictive factors.

	OR (95% CI)	*P*
Age	1.02 (1.00–1.04)	0.005
Sex (male)	1.65 (0.93–2.95)	0.085
Pre-conditional health		
Hypertension	2.07 (1.12–3.85)	0.02
MI	2.79 (1.28–6.06)	0.009
CVA	0.86 (0.31–2.42)	0.78
On-admission laboratory findings		
Total protein	0.6 (0.29–1.25)	0.1
Direct bilirubin	1.36 (0.81–2.3)	0.2
Albumin	0.39 (0.16–0.97)	0.04
LDH	1.00 (1.00–1.00)	0.2
PT	1.04 (0.98–1.11)	0.2
PTT	0.97 (0.94–1.01)	0.2

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; LDH, lactate dehydrogenase; MI, myocardial infarction; OR, odds ratio; PT, prothrombin time; PTT, partial thromboplastin time.

DISCUSSION

Given the paucity of research on the epidemiology of PTE and its associated factors in COVID-19 patients in Iran, the present study aimed to evaluate the epidemiological, clinical, and laboratory characteristics, as well as predisposing factors, of PTE patients who were also infected with COVID-19. Meta-analyses and retrospective studies reported the incidence of PTE as 40–70%. Respiratory tract infections, including COVID-19, are among the most significant predisposing factors for PTE. PTE was indicated to occur less than 30% of the time in patients with COVID-19. In line with previous studies on this subject, the incidence rate of PTE in patients with COVID-19 in the present study was 21.8%. Inflammatory processes, such as the cytokine storm and damage to lung endothelial cells caused by the coronavirus, which ultimately lead to pulmonary thrombosis, can be considered the leading causes of PTE in patients with COVID-19. As the findings of the present study indicate, among the demographic variables, patient age was significantly higher in patients with PTE than in those without PTE, which was confirmed by previous studies [6, 8, 17]. However, other studies have contradicted our findings [9, 18, 19]. The most common comorbidity in patients with PTE and COVID-19 was hypertension, followed by stroke and heart attack. These findings are similar to those of other studies in this field, which reported that the occurrence rates of these factors were significantly higher in the PTE group than in the non-PTE group [20-24]. In contrast to previous studies, the present study found no significant differences in the rates of malignancy [25-27] and DVT [28, 29] between the PTE and non-PTE groups infected with COVID-19. These differences could be attributed to the small sample size in our study. Miró *et al.* [17] confirmed our findings that oxygen saturation without a mask was significantly higher in the PTE group with COVID-19 than in the non-PTE group with COVID-19. The smoking rate in the PTE group was significantly higher than that in the non-PTE group, which is consistent with the findings of previous studies. Previous

Table 4. The multivariate logistic regression analyses of PTE risk factors.

	B	OR (95% CI)	*P*
Age	0.22	1.02 (0.99–1.05)	0.12
Albumin	-1.04	0.35 (0.13–0.92)	0.03

Abbreviations: CI, confidence interval; OR, odds ratio.

studies have indicated that the nicotine in cigarettes stimulates platelet-dependent coagulation, resulting in blood clotting and pulmonary embolism. Smoking can further increase the probability of PTE by increasing plasma fibrinogen levels, which in turn increase coagulation factor VIII levels [17, 30].

The findings of the present study indicate that the PTE group had significantly higher levels of AST and direct bilirubin than the non-PTE group. However, albumin levels were significantly lower, which is consistent with the results of previous studies. In patients with PTE, liver dysfunction is accompanied by a significant increase in AST and direct bilirubin levels and can be a consequence of tissue hypoxia caused by ischemic mechanisms (due to inadequate blood flow to the liver), arterial hypoxia (which leads to hepatocyte necrosis), and passive hepatic congestion, all of which ultimately lead to hepatic hypoxia [31-33]. Inflammation caused by COVID-19 in these patients could also explain changes in the levels of these factors [6, 31-34]. Other studies also confirmed higher PTT levels in the PTE group than in the non-PTE group [6, 35]. COVID-19-induced inflammation may lead to increased coagulation levels in PTE patients [6, 35]. In contrast to previous studies [18, 36], the levels of D-dimer, CRP, lactate dehydrogenase, white blood cells, and troponin in the PTE and non-PTE groups were not significantly different, which could be due to the small sample size of the present study.

This study is one of the few studies conducted on the epidemiology and risk factors of PTE in COVID-19 patients in Iran, and this can be regarded as one of the strengths of this research. Similar to other studies, the current study had some limitations, including a small sample size, the fact that it was conducted in a single center, and the lack of access to some evaluative parameters owing to its retrospective design. It is recommended that this type of study be conducted in the future with a larger sample size, data gathered from several centers, and a case-control design. It has also been suggested that advanced technologies be used for PTE prophylaxis, prevention, and tailored prescriptions [37].

CONCLUSION

The incidence rate of PTE was relatively high in patients with COVID-19, and was associated with underlying conditions such as blood pressure, heart attack, and stroke, as well as laboratory risk factors such as albumin, direct bilirubin, AST, and PTT levels. Regression analysis also showed that age, blood pressure, heart attack, and albumin levels were independent predictive factors for PTE development.

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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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