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The incidence, risk factors and clinical outcome of pulmonary embolism in hospitalized patients with COVID-19

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ABSTRACT

Objectives: Coronavirus-19 disease can cause a wide spectrum of diseases. One of the major mortal complications of the disease is hypercoagulable state, including life-threatening pulmonary embolism. COVID-19 infections may predispose venous thromboembolism due to excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation. The aim of this study was to evaluate the incidence and risk factors for pulmonary embolism in hospitalized patients with COVID-19 in Turkey and to determine the impact of pulmonary embolism on clinical outcomes.

Results: 69 patients who were hospitalized for COVID-19 pneumonia between 15 March and 30 April 2020 and underwent CT angiography on clinical suspicion were included in the study. All patients received at least standard doses thromboprophylaxis. The incidence of the PE was 24.4% (n = 17). In patients with pulmonary embolism a higher frequency of males (88% vs 61%, p = 0.013), higher rates of smoking (75% vs 37% ,p = 0.008) and chronic renal failure (19% vs 4%,p = 0.04) were noted. Pulmonary embolism was positively correlated with heart rate > 100 bpm (r = 0.479, p < 0.001), more than two fold increase in D-dimer (r = 0.421,p < 0.001) and active smoking (r = 0.323, p = 0.008).In three patients with pulmonary embolism, intensive care, non-invasive mechanical ventilation and intubation was required, mortality occurred only in 1 (6.0%) patient.

Conclusion: In our study, the frequency of pulmonary embolism in the patient population infected with COVID-19 was found to be 24.4%, despite effective DVT prophylaxis. It should be kept in mind that pulmonary embolism is one of the most common complications in patients hospitalized for COVID-19 infection.

Thrombotic complications in patients diagnosed with COVID-19 are emerging as important sequelae that contribute to significant morbidity and mortality [1, 2]. Pulmonary embolism (PE), deep vein thrombosis, ischemic stroke and myocardial infarction are examples of complications described in patients with increasing frequency [1, 2]. A hypercoagulable state is a common abnormality in patients with COVID-19, and is due to infection, inflammation, hypoxia, immobilization, and diffuse intravascular coagulation with marked elevations seen in lactate dehydrogenase, ferritin, C-reactive protein, D-dimer and interleukin levels [3,4]. Concomitant pulmonary embolisms have been detected

on the computed tomography (CT) scans of patients hospitalized mainly for respiratory symptoms due to COVID-19 [5, 6]. The purpose of this study was to evaluate the incidence of COVID-19 patients that developed pulmonary embolism and compare their clinical characteristics and inflammatory markers, D-dimer values and outcomes.

METHODS

Study population

A total of 69 patients (49 males, 59.2 (15.8) years) diagnosed with COVID-19 pneumonia at our hospital from March 15 to April 30, who had computed tomography pulmonary angiogram (CTPA) due to deterioration in clinical status or sudden drop in oxygen saturation during their follow-up were retrospectively included in this study.

The local ethics committee of Bursa Uludag University Hospital approved this retrospective study and waived the need of informed consent.

Assessments

Data on patient demographics (age, gender), hospitalization status, comorbidities, treatments and laboratory and echocardiography findings were retrieved from the Picture Archiving and Communication System (PACS) database. Initial report validated by a pulmonary medicine specialist as well as axial images of all CT cases with iodine contrast media injection were reviewed by the same radiologist. Simplified pulmonary embolism severity index (PESI) scores were calculated based upon clinical variables.

Imaging

CTPAs were acquired on 64+ row scanners after injection of 50 to 75 ml of high concentration iodine contrast media, with the use of a bolus-tracking technique and a threshold of 160HU to 250HU in the main pulmonary artery. Tension was fixed at 100kV and automatic tube-current modulation was used, with a maximum mAs varying between scanners but always below 350mAs. When possible, patients were instructed to hold their breath and raise their arms above their head to minimize artifacts. Images were reconstructed with a slice-thickness of 1 mm in mediastinal and parenchymal windows, and transmitted to post-processing workstations for multiplane and maximum intensity projection reconstructions. When identified, acute pulmonary embolism was classified as truncal, lobar, segmental or sub-segmental based on the location of the most proximal luminal defect during the entire examination.

The diagnosis of COVID-19 was based on positivity of RT-PCR analysis for SARS-Cov-2 or on presence of typical CT findings (i.e. extensive bilateral and peripheral ground glass opacities and/or alveolar consolidation) and compatible clinical data in RT-PCR-negative cases. Initial samples for RT-PCR analysis were obtained by nasopharyngeal swab, while a second or third sampling was required in some patients.

All patients in the study received a treatment protocol including hydroxychloroquine, azithromycin and prophylactic dose of low molecular weight heparin (LMWH).

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Chi-square ($\chi 2$) test was used for the comparison of categorical data, while independent sample t-test was used for analysis of the parametric variables. Pearson correlation analysis was used in the correlation analysis. Data were expressed as "mean ± standard deviation (SD), 95% confidence interval (CI) and percent (%) where appropriate. $p < 0.05$ was considered statistically significant

RESULTS

Baseline characteristics

The mean (SD) patient age was 59.2 ± 15.8 years and 49 of 69 patients were males. Of 69 patients diagnosed with COVID-19, 17(24.4%) had clinically relevant pulmonary embolism.

Pulmonary embolism was unilateral in (43.0%) cases and bilateral in 10 (57.0%) cases, while 9 patients had echocardiographically-confirmed pulmonary embolism findings (D-shape, increase in PAP), others had no serious pathological findings. When the radiological features of pulmonary embolism were analyzed, 35.7% were segmental, 14.3% were sub-segmental, 14.3% were truncal, and 35.7% were lobar.

Patient demographics and comorbidities in patients with vs. without pulmonary embolism

In patients with and without pulmonary embolism,

a significantly higher frequency of males (88% vs. 61%, p = 0.013) and higher rates of smoking (75% vs. 37%, p = 0.008) and chronic renal failure (19% vs. 4%, p = 0.049) were noted (Table 1).

No significant difference was noted in the mean age of patients with versus without pulmonary embolism (55.6 ± 18.1 vs. 60.1 ± 15.0 years, p > 0.05). COVID-19 positive patients with and without pulmonary embolism had similar rates of hypertension (25% vs. 24%), diabetes mellitus (19% vs. 16%), cardiovascular disease (19% vs. 18%), chronic heart failure (12% vs. 8%) (Table 1).

Laboratory findings in patients with vs. without pulmonary embolism

Troponin (36.8 ± 26.5 vs. 14.2 ± 20.8, p = 0.009) and ferritin (806.9 ± 683.2 vs 414.9 ± 419.8 ng/mL, p = 0.009) values were significantly higher in patients with vs. without pulmonary embolism. No significant difference was noted between the two groups in terms of other laboratory parameters, including D-dimer (2.38 ± 1.26 vs 4.13 ± 1.87) and CRP levels (65.7 ± 49.9 vs. 55.0 ± 42.3) (Table 2).

The risk of developing pulmonary embolism

Correlation analysis revealed that the likelihood of developing pulmonary embolism was positively correlated with heart rate of > 100 bpm (r = 0.479, p < 0.001), more than two-fold increase in D-dimer (r = 0.421, p < 0.001) and active smoking (r = 0.323, p = 0.008) (Table 3).

Table 1. Baseline characteristics in COVID-19 patients with vs. without pulmonary embolism

	COVID-19 patients (n = 69)		*p* value[1]
	Pulmonary embolism (+) (n = 17)	**Pulmonary embolism (-) (n = 52)**	
Demographics			
Age (years), mean ± SD	55.6 ± 18.1	60.1 ± 15.0	NS[2]
Gender (male), n (%)	15 (88.0)	31(61.0)	**0.013**
Smoking, n (%)	12(75.0)	19(37.0)	**0.008**
Comorbidities, n (%)			
Hypertension	4(25.0)	12 (24.0)	NS
Diabetes mellitus	3(19.0)	8(16.0)	NS
Cardiovascular disease	3(19.0)	9(18.0)	NS
Chronic heart failure	4(12.0)	4(8.0)	NS
Chronic renal failure	3(19.0)	2(4.0)	**0.049**

NS: Not significant
[1]Chi square test, [1]t-test

Table 2. Laboratory findings in COVID-19 patients with vs. without pulmonary embolism

	COVID-19 patients (n = 69)		*p* value
	Pulmonary embolism (+) (n = 17)	**Pulmonary embolism (-) (n = 52)**	
Laboratory findings, mean ± SD			
WBC (x1000/mm3)	5.07 ± 4.09	6.05 ± 4.18	NS
Hemoglobin (g/dL)	11.9 ± 3.7	10.3 ± 5.0	NS
Neutrophil (x1000/mm3)	4.9 ± 4.4	3.4 ± 2.9	NS
Lymphocyte (x1000/mm3)	1.3 ± 0.9	0.8 ± 0.6	NS
Glucose (mg/dL)	144.7 ± 43.3	130.0 ± 43.9	NS
GFR (mL/sec)	64.7 ± 35.5	67.6 ± 37.6	NS
AST (U/L)	23.5 ± 5.3	12.2 ± 4.7	**0.017**
ALT (U/L)	32.3 ± 24.4	36.0 ± 29.7	NS
Sodium (mmol/L)	137.6 ± 4.2	137.6 ± 3.2	NS
CRP (mg/ml)	65.7 ± 49.9	55.0 ± 42.3	NS
D-dimer (ng/mL)	2.38 ± 1.26	4.13 ± 1.87	NS
Ferritin (ng/ml)	806.9 ± 683.2	414.9 ± 419.8	**0.009**
Troponin	36.8 ± 29.5	14.2 ± 20.8	**0.009**

WBC: White blood cell; GFR: Glomerular filtration rate; AST: Aspartate aminotransaminase; ALT: Alanine aminotransaminase; CRP:C-reactive protein, NS: Not significant; t-test

Table 3. Correlation between pulmonary embolism and study parameters		
Variables		**Development of pulmonary embolism**
> 2-fold increase in D-dimer	N	69
	r	0.421
	p	**< 0.001**
Smoking	N	69
	r	0.323
	p	**0.008**
Heart rate > 100 bpm	N	69
	r	0.479
	p	**< 0.001**
Pearson correlation analysis, r: correlation coefficient		

Clinical outcomes in patients with vs. without pulmonary embolism

In three patients with pulmonary embolism, intensive care, non-invasive mechanical ventilation or intubation was required, while none of them died. In the group without pulmonary embolism, 2 patients had intubation need due to respiratory failure associated with ARDS and died (Table 4).

Accordingly, amongst the COVID-19 patients with pulmonary embolism, mortality occurred only in 1(6.0%) patient, due to massive pulmonary embolism and respiratory failure. In those without pulmonary embolism, 2(4.0%) patients died from respiratory failure due to ARDS. No significant difference was noted in mortality rates of COVID-19 patients with and without pulmonary embolism (6.0% vs. 4.0%, p > 0.05) (Table 4).

DISCUSSION

Our findings revealed the likelihood of developing pulmonary embolism among COVID-19 patients to be 24.4% (17/69) over a one-month period. This is in line with data from recent studies on the rates of pulmonary embolism (range, 23-30%) in COVID-19 patients who had CTPA in their follow up [7-9].

The remarkably high rates of pulmonary embolism in the current study, exceeding the rates reported in patients without COVID-19 infection, seems to indicate the association of COVID-19 with an increased risk of pulmonary embolism. In epidemiological studies, annual incidence rates for pulmonary embolism were reported to range from 39-115 per 100 000 population and for DVT to range from 53-162 per 100 000 population [10]. The frequency and severity of venous thromboembolic events are largely determined by genetic or acquired factors. Given that the presence of potential risk factors such as malignancy and previous surgical operations were amongst the exclusion criteria of the current study, it is noteworthy that the observed incidence was quite high. Indeed, high incidence of pulmonary embolism in COVID-19 patients in the literature has been considered to indicate an association between COVID-19 and venous thromboembolic disease [3, 11, 12].

Based on clinical studies, pulmonary embolism is considered to occur at 60 to 70 years of age in majority of cases, while autopsy data indicate the association of 70 to 80 years of age with the highest incidence [13]. In the current study, the mean age of total population was be 59.2(SD 15.8) years along with no significant difference in patients with vs. without pulmonary embolism in terms of age. The high rates of pulmonary embolism in a population without major risk factors seems to indicate the likelihood of COVID-19 per se to predispose development of venous thromboembolism, similar to activation of the coagulation system reported in other virus infections [14, 15]. In particular, coronavirus infections may trigger venous thromboembolism through participation of multiple pathogenic mechanisms such as endothelial

Table 4. Clinical outcomes in COVID-19 patients with vs. without pulmonary embolism			
	COVID-19 patients (n = 69)		***p* value**
	Pulmonary embolism (+) (n = 17)	**Pulmonary embolism (-) (n = 52)**	
Clinical outcomes, n(%)			
ICU stay	3 (16.0)	2(4.0)	NS
Mechanical ventilation need	2(12.0)	2(4.0)	NS
ARDS	0(0.0)	2 (0.04)	NS
CPAP need	1(6.0)	1(2.0)	NS
Mortality	1 (6.0)	2(4.0)	NS
ICU: Intensive care unit; ARDS: Adult respiratory distress syndrome; CPAP: Continuous Positive Airway Pressure; NS: Not significant [1]Chi square test			

dysfunction, characterized by increased levels of von Willebrand factor; systemic inflammation, by Toll-like receptor activation; and a procoagulant state, by tissue factor pathway activation [16]. In a subgroup of patients with severe COVID-19, high plasma levels of pro-inflammatory cytokines were reported [17]. The direct activation of the coagulation cascade by a cytokine storm is also possible. The development of severe hypoxemia in some patients with COVID-19 seems also notable given the evidence on facilitation of thrombus formation under hypoxic conditions as reported both in animal models of thrombosis and in humans [18]. The vascular response to hypoxia is controlled primarily by the hypoxia-inducible transcription factors, whose target genes include several factors that regulate thrombus formation [19]. Moreover, the indirect causes, such as immune-mediated damage by antiphospholipid antibodies, may partially contribute, as speculated by Zhang et al. [20]. However, our study revealed no findings supporting the immune-mediated damage.

Notably, our findings revealed no significant impact of concomitant pulmonary embolism on mortality rates in patients with COVID-19. In non-COVID-19 patient populations, mortality from acute pulmonary embolism has been reported to be as high as 30% if untreated, whereas to be 8% in diagnosed and treated cases [13]. Hence, in patients with COVID-19 mortality rates from pulmonary embolism seems to be lower than expected in other patient populations. This may be explained by the fact that all COVID-19 patients were hospitalized patients who were already receiving LMWH at prophylactic doses. A recent study reported that LMWH or unfractionated heparin (UFH) at prophylactic doses were associated with a reduced 28-day mortality in more severe COVID-19 patients displaying a sepsis-induced coagulopathy (SIC) score ≥ 4 (40.0% vs 64.2%, $p = 0.029$) or D-dimer levels > 6-fold higher than the upper limit of normal (32.8% vs 52.4%, $p = 0.017$) [21, 22]. In addition, administration of hydroxychloroquine sulfate in all of our patients may also have a beneficial effect, given that hydroxychloroquine sulfate was reported to be associated with reduction in incidence of fatal pulmonary embolism and venous thromboembolism in some studies (23-26). Hydroxychloroquine was also reported to reduce the red blood cell aggregation without prolonging the bleeding time along with a variably demonstrable reduction in platelet aggregation and blood viscosity in humans, while to reduce the thrombus size in experimental models [26].

In contrast the other studies, initial D-dimer values were high but similar in patients with and without pulmonary embolism in our study [9, 12, 27]. Although there was no significant difference between the two groups in terms of initial D-dimer values, the likelihood of more than 2-fold increase in D-dimer values from baseline was significantly higher in patients with pulmonary embolism. High values of D-dimer may be related to a higher activation of blood coagulation in COVID-19 patients secondary to a systemic inflammatory response syndrome or as a direct consequence of the SARS-CoV-2 itself. Features of disseminated intravascular coagulation (DIC) and pulmonary embolism, such as increase in D-dimer levels and fibrin degradation products, are highly prevalent in COVID-19 [28]. In a retrospective cohort study, elevated D-dimer levels (>1 g/L) were reported to be strongly associated with in-hospital mortality, and this relationship was maintained in multivariate analysis (OR 18.4, 95% CI 2.6–128.6; $p = 0.003$) [29]. Elevated D-dimer level on admission was not a significant determinant of pulmonary embolism in our cases. This may be related to the fact that D-dimer acts as an acute phase reactant in COVID-19. Therefore, continued D-dimer monitoring in patients may be important in predicting pulmonary embolism in COVID-19 infection.

Similar to previously reported distribution characteristics of pulmonary embolism in COVID-19 patients, most of pulmonary embolism cases were classified as segmental and sub-segmental in the current study [7]. Notably, in pulmonary embolism studies among patients without COVID-19, the location of embolus was generally reported to be proximal [30-32].

Chronic renal failure, male sex and smoking were risk factors for development of pulmonary embolism in the current study. Chronic diseases and heavy smoking are also risk factors of venous thromboembolism for normal population [33, 34]. In chronic kidney disease patients, mechanisms contributing to a pro-coagulant state include increased tissue factor, vWf, factor XIIa, VIIa, and fibrinogen levels along with reduced tissue plasminogen activator [35]. Data are conflicting as to whether male sex is a risk factor for pulmonary embolism; however, an analysis of national mortality data reported 20-30% higher mortality risk from pulmonary embolism among men than among women [36].

In approximately 16% of cases with pulmonary embolism, a transfer to ICU was required and need

for mechanical ventilator support was evident in two of these patients. No significant difference was noted in need for ICU stay or mechanical ventilator support, as well as in mortality rates between patients with and without pulmonary embolism. In contrast, a recently published study indicated the association of pulmonary embolism with increased risk of ICU admission and mechanical ventilation in COVID-19 patients [6]. This discrepancy may also be related to use of prophylactic doses LMWH and hydroxychloroquine sulfate in all of our patients.

Certain limitations to this study should be considered. First, we did not evaluate antithrombin 3, Protein C, S, and anticardiolipin antibody levels in each patient. Second, given that all patients were receiving prophylaxis in terms of venous thromboembolism, our findings may not reflect the incidence of pulmonary embolism in non-hospitalized COVID-19 patients.

CONCLUSION

In conclusion, approximately 24.4% of COVID-19 patients in the current study were diagnosed with pulmonary embolism, despite effective DVT prophylaxis. Development of pulmonary embolism seems not to affect mortality in COVID-19 patients who were under effective DVT prophylaxis. Therefore, use of contrast-enhanced thorax CT in monitoring of COVID-19 patients with low saturation seems to be a useful follow-up strategy, regardless of the risk factor status. It should be investigated whether the condition due to disease progression or comorbid pulmonary embolism, given that these patients can recover after effective treatment.

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