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Have the number of pulmonary embolism cases increased during the COVID-19 pandemic?

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Coagulation disorders, endothelial dysfunction, immobility and dehydration contribute to deep vein thrombosis (DVT) and pulmonary embolism (PE) in COVID-19 patients. While the prevalence of PE accompanying COVID-19 is high, the number of studies on its long-term effects is limited in literature.

Objectives. We expanded this process and aimed to evaluate a one-year period before and during the pandemic. We sought an answer to the question: "Is there a change in the frequency and clinical course of PE?"

Material and methods. Retrospectively, all patients admitted to our pulmonology clinic diagnosed with PE between October 2018–2019 (pre-pandemic) and April 2020–2021 (pandemic period) were included in the study. PE patients hospitalized due to COVID-19 infection were not included in the study.

Results. The prevalence of PE cases increased by 43% in the first year of the pandemic, and there was no significant difference in terms of symptoms, localisation and extent of thrombus in the pulmonary artery, DVT frequency, systolic pulmonary artery pressure (PABs) values, right heart load, frequency of thrombolytic therapy and mortality rates. A significant decrease was observed in predisposing factors of pulmonary embolism only in the postoperative period (7 patients (77.8%) before the pandemic; 2 patients (22.2%) during the pandemic; $p = 0.029$).

Conclusions. PE cases are encountered more frequently during the pandemic process, and no significant change was seen in patient's clinical findings and mortality.

Key words: pulmonary embolism, COVID-19, prognosis.

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Background

Pulmonary embolism (PE) is a significant health problem most frequently overlooked in clinical practice and is one of the most preventable causes of hospital mortality [1, 2]. The annual incidence of PE is 39–115 cases per 100,000. Mortality has been reported as being 30–35% in untreated patients [3, 4]. The coronavirus disease (COVID-19) caused by SARS-CoV-2, started in the last months of 2019, is also associated with an inflammatory and prothrombotic condition that increases the risk of thromboembolic events [5]. The risk of venous thromboembolism increases, especially in those with severe COVID-19, in the presence of cardiovascular disease, obesity, diabetes mellitus, arterial hypertension or other underlying diseases [6]. The mortality rate increases when vascular thrombosis occurs in COVID-19 patients [7].

Coagulation disorders, endothelial dysfunction, immobility and dehydration contribute to deep vein thrombosis (DVT), pulmonary embolism (PE) and systemic thrombosis in COVID-19 patients [8]. The interaction between inflammation, complement activation and coagulation cascade is crucial for understanding the pathophysiology of COVID-19 and is responsible for triggering disseminated intravascular coagulation (DIC). The deterioration of the intestinal barrier in COVID-19 patients also promotes systemic inflammation, leading to the emergence of a cytokine storm. The relationship between coagulation and inflammation also triggers disease progression and poor outcomes [9].

Acute pulmonary embolism (PE) is the most common thrombotic complication in COVID-19 patients [5]. During the COVID-19 pandemic, curfews were imposed in many countries, and COVID-19 patients were also treated in isolation at the hospital. On the other hand, some non-COVID-19 patients did not leave their homes for fear of contagion. Thus, immobility may be a risk factor for pulmonary embolism. Besides this, pneumonia itself is a risk factor for PE [10, 11]. It is thought that 'in situ' thrombosis develops secondary to inflammation rather than traditional thromboembolic disease patterns in COVID-19 patients [12].

In the meta-analysis of Desai et al., which included 3,066 patients, the prevalence of PE in COVID-19 patients was reported to be 15.8% [95% CI: 6.0–28.8%] [13]. Vlachou et al. also evaluated the risk of thrombotic in COVID-19 patients for at least four weeks before hospitalisation, before and after discharge, and found it to be 46.2% [14].

While examining the co-existence of COVID-19 and PE in the studies, only the frequency of PE in the two months before the pandemic and two months during the pandemic was compared in the study of Silva et al. An increase of 62% was found in the diagnosis of PE after the pandemic, and PE patients were reported as being older and with a lower prevalence of active cancer [15].

Objectives

We expanded this process and aimed to evaluate the one-year period before and during the pandemic. We sought an answer to the question: "Is there a change in the frequency and clinical course of PE?"

Material and methods

Retrospectively, all patients admitted to our pulmonology clinic with PE diagnosis between October 2018–2019 (pre-pandemic) and April 2020–2021 (pandemic period) were included in the study. PE patients hospitalized due to COVID-19 infection were not included in the study. The demographic characteristics of the patients, clinical findings, PE location on computed tomography (CT), ECO and lower extremity venous Doppler ultrasound (US) findings, need for thrombolytic therapy and treatment outcome was recorded. Ethics committee approval of our study was obtained from the Abant İzzet Baysal University Ethics Committee (date: 05.10.2021, no.: 238).

Data analysis was performed using the SPSS 18 statistical package program. Compliance with normal distribution was examined with the Kolmogorov-Smirnov test, the medians of the groups that did not show normal distribution were compared, and the Mann-Whitney U test was used for two independent groups. Chi-square, Fisher Exact and Cramer's V tests were used to analyse the categorical data. The effect size was examined by Cohen d (a helpful criterion in demonstrating clinical significance in addition to the statistical significance *p*-value in large samples). For significant parameters, the cut-off value was determined by Receiver Operative Characteristics (ROC) analysis. A *p*-value of < 0.05 was considered statistically significant.

Results

While the median age was 70 years (31–88) before the pandemic, it was 72 (30–90) during the pandemic ($p = 0.266$). No significant difference was found between the two groups in terms of gender ($p = 0.697$).

When the laboratory parameters of the two groups were compared, no significant difference was observed in terms of Troponin, C-reactive protein (CRP) and D-dimer values, and the neutrophil/lymphocyte ratio (NLR) was found to be lower in those with PE during the pandemic ($p = 0.029$) (Table 1). As a result of ROC analysis, the NLR parameter had a sensitivity of 86% in predicting embolism, and the cut-off value was determined as being 1.73 (AUC: 0.639, $p < 0.05$) (Table 2).

No significant difference was determined regarding symptoms, localisation and extent of thrombus in the pulmonary artery, frequency of DVT, systolic pulmonary artery pressure (PABs) values, right heart load, frequency of thrombolytic therapy and mortality rates (Table 3). When pulmonary embolism risk factors were compared, a significant difference was found only in the postoperative period (7 patients (77.8%) in the pre-pandemic period; 2 patients (22.2%) during the pandemic, $p = 0.029$, Table 3). PE cases were 43% higher than before the pandemic. It was determined that the duration of hospitalisation was shorter during the pandemic period ($p < 0.001$).

Table 1. Comparison of demographic, laboratory, echocardiographic findings and clinical findings of PE patients before and during the pandemic

	Pre-pandemic (*n* = 35, 41.2%)	During the pandemic (*n* = 50, 58.8%)	All patients (*n* = 85)	*p*[1]	Effect size Cohen d
Median (min–max)[1]					
Age	70 (31–88) 67.23 ± 17.08	73 (30–90) 72.24 ± 12.93	72 (30–90) 70.18 ± 14.89	0.266	–
Duration of hospitalisation (days)	8 (3–21)	5 (1–17)	6 (1–21)	**0.000***	0.99
Troponin (ng/L)	22 (1.3–250)	10 (0.2–701)	13 (0.2–701)	0.955	–
PABs (mm Hg)	21.5 (20–77)	35 (15–95)	34 (15–95)	0.941	–
D-Dimer (mg/L)	3.26 (0.19–24.11)	5.76 (0.23–1636)	4 (0.19–1636)	0.077	–
CRP (mg/L)	36.6 (0.10–187.30)	29.30 (0.10–168.9)	30.7 (0.10–187.30)	0.277	–
NLR	4.08 (1.17–30.25)	2.46 (0.66–8.01)	2.89 (0.66–30.25)	**0.029***	0.61
SpO_2	93.20 (75.5–98.6)	93.2 (80–98)	93.2 (75.5–98.6)	0.881	–

[1] Mann-Whitney U test, * statistically significant, CRP – C-reactive protein, PABs – pulmonary artery systolic pressure, NLR – neutrophil/lymphocyte ratio, SpO_2 – pulse oxygen saturation.

Table 2. ROC analysis of laboratory findings

	AUC (%95 CI)	Cut-off	*p*	Sensitivity (%)	Specificity (%)
CRP (mg/L)	0.430 (0.300–0.559)	–	0.277	–	–
Troponin (ng/L)	0.496 (0.337–0.654)	–	0.955	–	–
D-Dimer (mg/L)	0.620 (0.494–0.745)	–	0.077	–	–
NLR	0.639 (0.511–0.768)	1.730	**0.029***	86.0	20.0

* Statistically significant, CRP – C-reactive protein, NLR – neutrophil/lymphocyte ratio.

Table 3. Comparison of patients' symptoms, underlying predisposing factors, location and extent of thrombus, Doppler US and treatment

	Pre-pandemic (*n* = 35; 41.2%)	During pandemic (*n* = 50; 58.8%)	General (*n* = 85)	*p*[a]
Gender female male	 19 (43.2%) 16 (39.0%)	 25 (56.8%) 25 (61.0%)	 44 (51.8%) 41 (48.2%)	0.697

Table 3. Comparison of patients' symptoms, underlying predisposing factors, location and extent of thrombus, Doppler US and treatment

	Pre-pandemic (*n* = 35; 41.2%)	During pandemic (*n* = 50; 58.8%)	General (*n* = 85)	*p*[a]
Comorbidity yes no	 25 (37.3%) 10 (55.6%)	 42 (62.7%) 8 (44.4%)	 67 (78.8%) 18 (21.2%)	 0.163
Postoperative period	7 (77.8%)	2 (22.2%)	9 (10.6%)	**0.029***[,b]
Malignancy	5 (33.3%)	10 (66.7%)	15 (17.6%)	0.496
Genetic disorder	1 (33.3%)	2 (66.7%)	3 (3.5%)	1.000[b]
Recurrent embolism	3 (42.9%)	4 (57.1%)	7 (8.2%)	1.000[b]
CVS disease	11 (29.7%)	26 (70.3%)	37 (43.5%)	0.060
Obesity	0 (0%)	1 (100%)	1 (1.2%)	1.000[b]
Idiopathic (unknown risk factor)	7 (41.2%)	10 (58.8%)	17 (20%)	1.000
Dyspnoea	25 (36.8%)	43 (63.2%)	68 (80%)	0.098
Chest pain	9 (47.4%)	10 (52.6%)	19 (22.4%)	0.534
Haemoptysis	0 (0%)	4 (100%)	4 (4.7%)	0.140[b]
Syncope	1 (50.0%)	1 (50.0%)	2 (2.4%)	1.000[b]
Oedema in the leg	0 (0%)	2 (100%)	2 (2.4%)	0.510[b]
Thrombus location main pulmonary lobar segmental	 13 (40.6%) 8 (30.8%) 14 (51.9%)	 19 (59.4%) 18 (69.2%) 13 (48.1%)	 32 (37.6%) 26 (30.6%) 27 (31.8%)	 0.296
Thrombus diffuseness unilateral bilateral	 17 (44.7%) 18 (38.3%)	 21 (55.3%) 29 (61.7%)	 38 (44.7%) 47 (55.3%)	 0.549
Had DVT non-DVT not requested	6 (35.3%) 16 (40.0%) 13 (46.4%)	11 (64.7%) 24 (60.0%) 15 (53.6%)	17 (20%) 40 (47.1%) 28 (32.9%)	 0.747
Right heart dilatation	3(37.5%)	5 (62.5%)	8 (11.4%)	0.719[b]
Given thrombolytic	12 (60.0%)	8 (40.0%)	20 (23.5%)	0.050
Treatment given upon discharge LMWH warfarin sodium DOAK	 12 (46.2) 7 (87.5) 14 (28.6%)	 14 (53.8) 1 (12.5%) 35 (71.4%)	 26 (31.3%) 8 (9.6%) 49 (59%)	 **0.005**[b]
Mortality	2 (5.7%)	0 (0%)	2 (2.4%)	0.167[b]

* Statistically significant, [a] Chi-square test, [b] Fisher Exact test, [c] Cramer's V, DVT – deep vein thrombosis, LMWH – low molecular weight heparin, DOAC – direct oral anticoagulant.

Discussion

While the co-existence of COVID-19 and PE is common, studies investigating the frequency of PE before and after the pandemic are limited in literature. When Silva et al. compared the PE frequency two months before the pandemic and two months during the pandemic, it was reported that there was a 62% increase in the diagnosis of PE after the pandemic and that the patients were older [15]. In our study, PE cases were found to increase by 43% in the first year of the pandemic, and there was no significant age difference between the groups (Figure 1).

Silva et al. reported that PE cases had a lower prevalence of active cancer after the pandemic [15]. In this study, the postoperative period, one of the predisposing factors, was found to be less often during the pandemic process. Elective surgical procedures were cancelled or postponed during the pandemic period due to the increased risk of nosocomial infection in surgical patients and the possibility of susceptibility to infection due to the stress of surgery and anaesthesia. İlhan et al. also reported a significant decrease in the number of elective operations [16]. Kılıç et al. reported a 52.6% decrease in orthopaedic surgery cases compared to the pre-pandemic period [17]. Based on this data, we think that the number of applicants in the postoperative period has decreased.

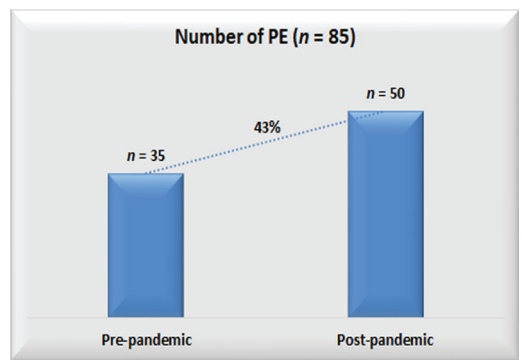

Figure 1. Comparison of the rates of pre-pandemic and post-pandemic PE patients

We found no significant difference between the two groups in PE symptoms and laboratory findings other than NLR. NLR was lower in those with PE detected during the pandemic ($p = 0.029$). As a result of ROC analysis, the NLR parameter had a sensitivity of 86% in predicting embolism, and the cut-off value was determined as being 1.73 (AUC: 0.639, $p < 0.05$). High NLR level was associated with poor prognosis and increased inflammation in diseases [18, 19]. NLR is an independent prognostic

factor used to identify high-risk patients and predict mortality in PE [18]. In studies, cut-off values for NLR were reported in the range of 5.70–9.2 [20]. Since we only had two patients who died in our study, we could not statistically evaluate its relationship with mortality. However, both patients who died were in the pre-pandemic period and we did not encounter any deaths during the pandemic period.

D-Dimer, a fibrin degradation product, is immediately elevated in PE, as well as in coagulopathy in COVID-19 patients [21]. Our study found no significant difference between the two groups regarding D-Dimer levels.

Although concomitant thrombotic lesions in COVID-19 patients are primarily detected in segmental and subsegmental arteries [12], in our study (patients with COVID-19 accompanying PE were not included in the study), we did not find any change in the localisation and prevalence of PE during the pandemic. Although the bilateral prevalence and main pulmonary-lobar involvement were high, this was not statistically significant. Accordingly, we did not determine any significant change in mortality with echocardiographic findings (PAPs and right ventricular load), and thus thrombolytic administration. However, the shorter hospitalisation period for PE during the pandemic might be due to the fact that we used a direct oral anticoagulant (DOAC) instead of Warfarin sodium in the treatment, which does not require strict laboratory follow-up and does not require a long time to increase the effective dose. We also aimed to discharge patients as soon as possible to protect them from possible COVID-19 transmission in the hospital.

We found that only 4 of the PE patients during the pandemic had COVID-19 (SARS-CoV2 PCR positive). While 1 of these patients did not have any comorbid diseases, 1 had chronic obstructive pulmonary disease (COPD), and 2 had cardiovascular system diseases. All 4 patients were admitted with dyspnoea, and it was observed that they had bilaterally dispersed thrombi, half of which were located in the lobar and half in the main pulmonary artery. All patients recovered without the need for thrombolytic therapy. Statistical analysis could not be performed due to the small number of patients.

Limitations of the study

The limitations of this study are the small number of patients, since the study was performed in a single centre, although we compared the two groups for one year. However, our study reveals that PE cases have increased during the pandemic process, and there was no difference regarding PE symptoms, signs and mortality.

Conclusions

During the pandemic, PE cases were encountered more frequently, yet no significant change was found in the clinical findings and mortality of the patients. Larger patient data are needed to determine the risks for how long and to what extent COVID-19 poses.

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