SARS-CoV-2 antibody research in patients with unprovoked pulmonary embolism in COVID-19 pandemic period

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Abstract

Objective Due to the coronavirus disease 2019 (COVID-19) pandemic, a significant increase has been observed in patients diagnosed with pulmonary embolism (PE) in our clinic. In addition to COVID-19-related PE, the increase in the number of patients with unprovoked or idiopathic PE was also noteworthy. Although it is not surprising that PE due to immobilization was observed in elderly patients and patients with comorbidities at risk for PE during the pandemic, it is important to investigate the increase in the number of unprovoked PE. Thus, we aimed to show that a previous COVID-19 infection may be a risk factor in these patients by examining the presence of severe acute respiratory syndrome-causing coronavirus (SARS-CoV-2) antibodies in patients diagnosed with unprovoked PE.

Materials and methods The participants of the study consisted of 45 consecutive patients who were diagnosed with PE in our clinic, had no risk factors for PE, were considered unprovoked (idiopathic) PE, and had no history of COVID-19. SARS-CoV-2 antibody titers were measured in the serum samples of the patients for detecting immunity as a result of encountering COVID-19.

Results Of the 45 patients diagnosed with PE, 24 (53.3%) patients were diagnosed with computed tomography pulmonary angiogram (CTPA), and 21 (46.7%) patients were diagnosed with perfusion single-photon emission computed tomography (Q-SPECT/CT). Immunity acquired after encountering COVID-19 was checked with the NCP kit, which revealed positive results in 9 (20%) patients.

Conclusion It should be kept in mind that some of the patients diagnosed with idiopathic PE during the pandemic may have embolism due to asymptomatic COVID-19. In addition, it is now known that COVID-19 also creates a tendency toward thrombosis in asymptomatic patients.

Keywords Antibody · Antigen · COVID-19 · SARS-CoV-2 · Pulmonary thromboembolism · Tomography · PE

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Abbreviations

COVID-19	Coronavirus Disease 2019.
CTPA	Computerized tomography pulmonary angiography.
DVT	Deep Vein Thrombosis.
ECHO	Echocardiography.
NCP	Anti-nucleocapsid.
PE	Pulmonary Embolism.
Pro-BNP	B-type Natriuretic Peptide.
Q-SPECT/CT	Perfusion Single-Photon Emission Computerized Tomography / Computerized Tomography.
rtPCR	Reverse Transcription Polymerase Chain Reaction.
SARS-CoV-2	Severe Acute Respiratory Syndrome

causing Coronavirus.

VTE   Venous Thromboembolism.

Introduction

Acute pulmonary embolism (PE) is a serious and mortal disease with a prevalence that varies between countries [1]. In the pathophysiology of the disease, three factors defined by Virchow in 1856 are predicted to cause intravascular coagulation, which predisposes patients to thrombus: vascular endothelial damage, hypercoagulability, and stasis [2]. 75% of the cases of venous thromboembolism (VTE) have acquired and/or hereditary factors that lead to one of these three factors [3]. Major risk factors for PE include cancer, immobilization, pregnancy, obesity, and estrogen supplementation [4]. Nevertheless, it is possible that some patients with PE do not have an identifiable risk factor, which represents approximately 33% of the patients diagnosed with PE [5]. With the emergence of the coronavirus disease 2019 (COVID-19) pandemic, an increase has been observed in this condition, which is defined as unprovoked (idiopathic) PE in our clinic.

The COVID-19 pandemic has been associated with a significant increase in thrombotic events, such as deep vein thrombosis, PE, and systemic thrombosis [6–8]. The disease can do this to every component in the Virchow triad [1]. These complications are common in patients with severe COVID-19, and the presence of PE has been demonstrated in asymptomatic cases as well [9]. Accordingly, we hypothesized that the increased incidence of idiopathic PE during the pandemic in our clinic may be due to asymptomatic undiagnosed COVID-19 infection. Thus, we aimed to show that a previous COVID-19 infection may be a risk factor in these patients by examining the presence of severe acute respiratory syndrome-causing coronavirus (SARS-CoV-2) antibodies in patients diagnosed with unprovoked PE.

Materials and methods

Study design and settings

The study participants were 45 consecutive patients who have admitted to the chest-diseases outpatient clinic between June 1, 2021, and October 1, 2021, and were diagnosed with PE by radiological or scintigraphic methods. In all cases, the PE was accepted as unprovoked (idiopathic) due to the absence of any predisposing factors. The participants gave voluntary consent to participate in the study. Serum samples were obtained from the patients. The plan was to test for COVID antibodies in the medical microbiology

laboratory using SARS-CoV-2 anti-nucleocapsid (NCP) IgG and SARS-CoV-2 anti-spike IgG tests in serum. The study was approved by the university ethics committee (18.06.2021- E-23786442-604.01.02-137468).

Participants

The participant inclusion criteria were the following:

- Age greater than 18 years.
- A diagnosis of pulmonary embolism by perfusion single-photon emission computerized tomography/computerized tomography (Q-SPECT/CT) or computerized tomography pulmonary angiography (CTPA).
- A negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test performed simultaneously with the diagnosis of embolism.

The participant exclusion criteria were:

- Age less than 18 years.
- Not signing the consent form.
- A history of COVID-19 infection.
- Vaccination for COVID-19.
- Any of the following risk factors:

  Hospitalization for lower extremity fracture, heart failure, or atrial fibrillation/flutter (in the last 3 months), hip or knee prosthesis, major trauma, previous myocardial infarction in the last 3 months, previous VTE, spinal cord injury, arthroscopic knee surgery, blood transfusion, central venous catheter, intravenous catheters, chemotherapy, congestive heart failure or respiratory failure, erythropoiesis stimulating agents, hormone replacement therapy, in vitro fertilization, oral contraceptive therapy, postpartum treatment, inflammatory bowel disease, cancer (high risk in the presence of metastases), paralytic stroke, superficial vein thrombosis, prolonged sitting still (airplane or car trip), laparoscopic surgery, obesity, pregnancy, and varicose veins.

Data collection

Demographic characteristics (age, gender), anthropometric data (height, weight, body mass index), chronic diseases, smoking history, COVID-19 or contact history, and vaccination history were obtained from the patients included in the study. Embolism diagnostic methods, presence of lower extremity deep vein thrombosis (DVT), echocardiography

(ECHO) findings, D-dimer, pro-B-type natriuretic peptide (pro-BNP), and troponin-T levels were recorded.

SARS-CoV-2 IgG NCP antibody test

Approximately 3 ml of blood were collected from the participants in vacuum tubes containing separator gel and centrifuged at 5000rpm for 5min. The obtained serum was then divided into microcentrifuge tubes in accordance with the manufacturer's instructions (Abbot, Illinois, USA) and incubated at -20°C until testing. Serum samples were thawed at room temperature on the day of the test and prepared for use. All reagents in the Abbott SARS-CoV-2 IgG NCP antibody kit with the CMIA test method were brought to room temperature (+18 to 25°C) approximately 30min before use.

The test was carried out using a closed fully automated system (Architect i1000SR, Abbott, USA). The Abbot SARS-CoV-2 IgG NCP kit was used in accordance with the stated test instructions. The average chemiluminescent signal of the three calibrators in the test was calculated by the Architect instrument, and results divided by the output value of the sample are reported. The default unit of a result for the SARS-CoV-2 IgG test is the Index (S/C), where < 1.4S/C indicates a negative result, and ≥ 1.4S/C indicates a positive result.

SARS-CoV-2 IgG II quant antibody test

The stored serum samples were removed from the −20°C freezer on the day of the test and allowed to reach room temperature. The reagents in the Abbott SARS-CoV-2 IgG II Quant antibody kit with the CMIA test method were brought to room temperature (+18 to 25°C) approximately 30min before use. The test was executed using a closed fully automated system (Architect i1000SR, Abbott, USA). The 4-Parameter Logistic Curve method (4PLC, Y-weighted) was used to determine the calibration value and the results of the sample serums with the AdviseDx SARS-CoV-2 IgG II assay. These values were calculated quantitatively.

The unit of a result for the AdviseDx SARS-CoV-2 IgG II test is AU/mL (Arbitrary Unit/mL), and the cutoff value is 50.0 AU/mL. In the results, < 50.0 AU/mL was interpreted as negative, and ≥ 50.0 AU/mL was interpreted as positive. In addition, a multiplication was performed with a BAU/mL (Binding Antibody Unit/mL) coefficient of 0.142 according to the standard unit recommended by the World Health Organization. In this framework, < 7.1 BAU/mL was evaluated as negative, and ≥ 7.1 BAU/mL was evaluated as positive.

Statistical analysis

All analyses were performed in SPSS v21 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of quantitative variables was checked with the Kolmogorov-Smirnov test. Quantitative variables are summarized as the mean ± standard deviation, while qualitative variables are summarized as frequency (percentage) values.

Results

Participants

There were 125 patients diagnosed with PE in our outpatient clinic between June 1, 2021, and October 1, 2021, and 48 of them met the study's inclusion criteria. Three patients who did not provide voluntary consent were excluded, and a total of 45 patients were eventually included.

Demographic data

Of the 45 participating patients, 21 (46.6%) were female, and 24 (53.7%) were male. The mean age of the patients was 54.4 ± 16.4 years, and 28.9% of the patients had no comorbidities. The mean BMI of all patients was 27.9 ± 3.6. In terms of smoking, 24 (53.3%) patients had never smoked, 12 (26.7%) were ex-smokers, and 9 (20%) patients were active smokers (Table 1).

Among the 9 patients who were positive for SARS-Cov-2 NCP, 4 (44.4%) patients were female, and 5 (55.6%) were male. The mean age of the patients was 55.7 ± 12.1 years, and the mean BMI was 24.2 ± 3.0. In terms of smoking, 3 (33.3%) patients had never smoked, 6 (66.7%) were ex-smokers, and 0 (0.0%) patients were active smokers (Table 1).

Diagnostic parameters

While 24 (53.3%) of the patients were diagnosed with PE with CTPA, 21 patients (46.7%) were diagnosed with the Q-SPECT/CT technique. Among patients diagnosed with CTPA, 7 (15.6%) showed main pulmonary defects, 5 (11.1%) showed lobar defects, 11 (24.4%) showed segmental defects, and 1 (2.2%) showed multiple sub-segmental filling defects. Among patients diagnosed with Q-SPECT/CT, 2 (4.4%) had lobar, 9 (20.0%) had segmental, and 10 (22.2%) had sub-segmental defects. At the time of diagnosis, 7 (15.6%) patients had signs of right heart loading on ECHO. Deep vein thrombosis was detected in 3 (6.7%) patients using lower-extremity venous Doppler ultrasonography (USG) (Table 1).

Table 1 Clinical and demographic features of the study population

	All Patients (n = 45)	NCP positive (n = 9)
Age (year), mean ± SD	54.4 ± 16.4	55.7 ± 12.1
Sex, n (%)	21 (46.6%)	4 (44.4%)
Female	24 (53.3%)	5 (55.6%)
Male		
Body Mass Index (kg/m²), mean ± SD	27.9 ± 3.6	24.2 ± 3.0
Comorbidities, n (%)	13 (28.9%)	4 (44.4%)
No	32 (71.1%)	5 (55.6%)
Yes	12 (26.7%)	1 (11.1%)
Diabetes Mellitus	15 (33.3%)	2 (22.2%)
Hypertension	8 (17.7%)	0 (0%)
Hyperlipidemia	3 (0.66%)	0 (0%)
Coronary Arter Diseases	15 (33,3%)	1 (11.1%)
Drug history	0 (0%)	0 (0%)
Anti-platelet		
Anti-coagulant		
Smoking classification, n (%)	24 (53.3%)	3 (33.3%)
Never smoker	12 (26.7%)	6 (66.7%)
Ex-smoker	9 (20%)	0 (0.0%)
Smoker		
Smoking (pack-year) mean ± SD	17.9 ± 30.3	26.8 ± 36.4
PE diagnosis, n (%)	24 (53.3%)	4 (44.4%)
CTPA	7 (15.6%)	1 (11.1%)
Main pulmonary artery	5 (11.1%)	1 (11.1%)
Lobar	11 (24.4%)	2 (22.2%)
Segmental	1 (2.2%)	0 (0.0%)
Sub-segmental	1 (2.2%)	0 (0.0%)
≥2 sub-segment	21 (46.7%)	5 (55.6%)
Q-SPECT/CT	2 (4.4%)	0 (0.0%)
Lobar	9 (20.0%)	3 (33.3%)
Segmental	10 (22.2%)	2 (22.2%)
Sub-segmental	10 (22.2%)	2 (22.2%)
≥2 sub-segment		
Pro-BNP (pg/ml), mean ± SD	1029.1 ± 5204.2	314.8 ± 508.2
Troponin-T (ng/ml), mean ± SD	4.1 ± 12.3	8.3 ± 18.4
D-dimer (mg/L), mean ± SD	2.5 ± 5.5	1.1 ± 0.7
Deterioration of right heart functions in ECHO	38 (84.4%)	8 (88.9%)
No	7 (15.6%)	1 (11.1%)
Yes		
DVT, n (%)	42 (93.3%)	9 (100.0%)
No	3 (6.7%)	0 (0.0%)
Yes		
WBC (10^3/Ml)	6.71 ± 2.45	7.23 ± 3.15
HGB (g/dl)	12.21 ± 2.40	12.48 ± 2.81
HCT (%)	37.65 ± 4.96	38.25 ± 3.79
PLT (10^3/Ml)	253.45 ± 85.12	245.78 ± 50.36
CRP (mg/L)	18.97 ± 8.25	19.2 ± 4.26
Pulmonary embolism therapy drug	5 (11.1%)	1 (20%)
Oral anticoagulants	40 (89.9%)	4 (80%)
Low molecular weight heparin		
Spike AV/ML, mean ± SD	2999.7 ± 8877.9	2543.1 ± 4373.5
Spike BAV/ML, mean ± SD	416.0 ± 1261.4	361.1 ± 621.0
Spike n (%)	17 (37.8%)	0 (0.0%)
Negative	28 (62.2%)	9 (100%)
Positive		
NCP S/CO, mean ± SD	0.7 ± 1.37	3.15 ± 1.36
NCP, n (%)	36 (%80)	
Negative	9 (%20)	
Positive		

Abbreviations-: CTPA: Computerized tomography pulmonary angiography, ECHO: Echocardiography, NCP: Anti-nucleocapsid, Q-SPECT/CT: Perfusion Single-Photon Emission Computerized Tomography / Computerized Tomography

Among SARS-CoV-2 NCP-positive patients, 4 (44.4%) patients were diagnosed with PE by CTPA, while 5 patients (55.6%) were diagnosed with the Q-SPECT/CT technique. In patients diagnosed with CTPA, 1 (11.1%) had main pulmonary, 1 (11.1%) had lobar, and 2 (22.2%) had segmental filling defects. Among patients diagnosed with Q-SPECT/CT, 0 (0.0%) had lobar, 3 (33.3) had segmental, and 2 (22.2) had multiple sub-segmental perfusion defects. At the time of diagnosis, 1 (11.1%) patient showed signs of right heart loading on ECHO. DVT was not detected in any of the NCP-positive patients (Table 1).

Clinical and laboratory parameters

At the time of diagnosis, the mean D-dimer level of all patients was 2.5 ± 5.5 mg/L, and the mean pro-BNP level was 1029.1 ± 5204.2 pg/ml. The mean troponin T level was 4.1 ± 12.3 ng/ml (Table 1). For NCP-positive patients, the mean D-dimer level was 1.1 ± 0.7 mg/L, the mean pro-BNP level was 314.8 ± 508.2 pg/ml, and the mean troponin T level was 8.3 ± 18.4 ng/ml (Table 1).

Immunity acquired after encountering COVID-19 was checked with the NCP kit, which revealed positive results in 9 (20%) patients (Table 1). D-dimer elevation was present in 7 (77.7%) of these patients. The mean NCP value of 45 patients with PE in the study was found to be 0.7 ± 1.37 S/CO, while the mean NCP value of 9 NCP-positive patients was 3.15 ± 1.36 S/CO (Table 1).

Discussion

The aim of the present study is to show that COVID-19 may actually be a predisposing factor in some of the patients diagnosed with unprovoked PE who had no risk factors during the pandemic. The results showed that 9 (20%) of the 45 patients were asymptomatic and had COVID-19 without a diagnosis. In the literature, the frequency of PE due to COVID-19 has been reported to range from 24 to 35% [10, 11]. In a prospective study by Jevnikar et al., PE was diagnosed with CTPA in 19 of 106 (14.2%) consecutive patients at the time of first hospital admission with COVID-19 [12]. In a multicenter study by Riyahi et al., the rate of PE was found to be 25% in patients hospitalized for COVID-19 [13]. Therefore, it is an expected finding that the frequency of PE diagnosis increases with the pandemic. Minuz et al. stated that there was an increase in the incidence of PE during the pandemic period compared to the previous 3 years and reported that some of these diagnoses were PE due to COVID-19 [10].

The majority of COVID-19 cases were asymptomatic and mild during the pandemic [14]. Although the tendency for thrombosis in hospitalized and severe COVID-19 cases was first noticed, research later revealed that this was not only related to the severity of the disease but also a tendency toward thrombosis in mild cases [2, 9, 11, 15, 16]. In fact, there is insufficient data in the literature regarding the frequency of asymptomatic COVID-19 and the tendency toward thrombosis in this group, although it has been stated that PE can be encountered even in asymptomatic cases [9, 17]. Our study also supports the finding that asymptomatic SARS-CoV-2 infection increases the tendency toward thrombosis.

Previous studies reported that the incidence of idiopathic PE was 16.5% and 51% [5, 18]. This rate was found to be 36% in our study. The present study is the first to investigate COVID-19 as a risk factor for idiopathic embolism.

Few cases have been described in the literature of patients who had asymptomatic or unusual symptoms of COVID-19 and no known risk factor for thromboembolic disease and then exhibited extensive acute PE [19, 20]. No massive pulmonary embolism was detected in any of our patients. Since 18 patients were diagnosed with submassive (low PESI score) and 27 patients with a non-massive clinical condition, none of the patients needed reperfusion therapy. Submassive PE patients were treated as inpatients, while non-massive patients were treated as outpatients. American Society of Hematology and the International Society of Thrombosis and Hemostasis recommend using therapeutic anticoagulation in hospitalized patients. These guidelines mostly focus on acutely ill hospitalized patients but anticoagulation in asymptomatic or non-hospitalized patients is not well documented [21, 22]. While treatment with LMHH was started in 40 of 45 patients diagnosed with pulmonary embolism, 5 of them used the oral anticoagulant Rivaroxaban.

The only limitation of our study is the small number of patients. However, the sample size is sufficient as the present study is a single-center study and includes cases of unprovoked PE and unvaccinated patients with COVID-19. The strongest aspect of our study is that it is the first study to examine the relationship with COVID-19 in patients with unprovoked PE. The present study holds importance because it supports the notion that there has been an increase in the frequency of idiopathic PE due to the pandemic and shows that symptomatic COVID-19 can also cause PE.

Conclusion

Even if patients diagnosed with idiopathic PE do not have a history of COVID-19, the etiology of PE may be asymptomatic and involve a history of COVID-19. It should be kept in mind that some of the patients diagnosed with

idiopathic PE during the pandemic may have embolism due to asymptomatic COVID-19. In addition, it is now known that COVID-19 also creates a tendency toward thrombosis in asymptomatic patients.

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