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Relationship Between Asymptomatic COVID-19 and Pulmonary Embolism: Case-Control Study

Asemptomatik COVID-19 ve Pulmoner Emboli İlişkisi: Olgu-Kontrol Çalışması

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ABSTRACT Objective: The incidence of pulmonary embolism (PE) has increased in coronavirus disease-2019 (COVID-19) infection. The aim of study is to determine whether there is an increase in the frequency of PE in asymptomatic COVID-19 patients. **Material and Methods:** Patients who were diagnosed with PE our hospital, who did not have COVID-19 and who were not vaccinated against COVID-19 were included in the study group and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) antibody levels were examined. The control group was consisted of patients who did not have PE, had not had COVID-19 and were not vaccinated and SARS-CoV-2 antibody levels were examined. The antibody positivity rates, antibody titer levels of both groups were compared. **Results:** A total of 32 patients, 16 in the study group and 16 in the control group, were included in the study. Of all patients, 22 (68.8%) were male, 10 (31.3%) were female. While the mean age of men was 47.36±14.86, women was 51±24.463 (p=0.671). There was no statistically difference between the 2 groups in terms of mean age (p=0.346). When the groups were compared in terms of SARS-CoV-2 antibody, antibody positivity was found in 7 (43.8%) patients in both the study group and the control group (p=1.000). There wasn't difference between the groups antibody titers (p=0.275). The rate of asymptomatic COVID-19 infection in patients with PE was found to be similar to the population followed with non-PE diagnoses. **Conclusion:** The results of study show that there is no increase in the risk of PE in patients with asymptomatic COVID-19 infection.

Keywords: COVID-19; pulmonery embolism

ÖZET Amaç: Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonunda pulmoner emboli (PE) insidansı artmıştır. Çalışmanın amacı asemptomatik COVID-19 hastalarında PE sıklığında artış olup olmadığını belirlemektir. **Gereç ve Yöntemler:** Hastanemizde PE tanısı alan, COVID-19 olmayan ve COVID-19 aşısı olmayan hastalar çalışma grubuna alındı ve şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV)-2) antikor seviyelerine bakıldı. Kontrol grubu PE olmayan, COVID-19 geçirmemiş ve aşılanmamış hastalardan oluşturuldu ve SARS-CoV-2 antikor düzeyleri bakıldı. Her iki grubun antikor pozitiflik oranları, antikor titre düzeyleri karşılaştırıldı. **Bulgular:** Çalışma grubuna 16, kontrol grubuna 16 olmak üzere toplam 32 hasta dahil edildi. Tüm hastaların 22'si (%68,8) erkek, 10'u (%31,3) kadındı. Erkeklerin yaş ortalaması 47,36±14,86 iken kadınların 51±24,463'tür (p=0,671). Yaş ortalamaları açısından 2 grup arasında istatistiksel olarak fark yoktu (p=0,346). Gruplar SARS-CoV-2 antikoru açısından karşılaştırıldığında hem çalışma grubunda hem de kontrol grubunda 7 (%43,8) hastada antikor pozitifliği saptandı (p=1.000). Gruplar arasında antikor titreleri arasında fark yoktu (p=0,275). PE'li hastalarda asemptomatik COVID-19 enfeksiyonu oranı, PE olmayan tanılarla takip edilen popülasyona benzer bulundu. **Sonuç:** Çalışmanın sonuçları asemptomatik COVID-19 enfeksiyonu olan hastalarda PE riskinde artış olmadığını göstermektedir.

Anahtar Kelimeler: COVID-19; pulmoner emboli

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Coronavirus disease-2019 (COVID-19) infection is an infection caused by the new severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus, which can cause fatal infections, especially in the lower respiratory tract. Symptom scale can range from asymptomatic to acute respiratory distress syndrome.[1,2] In the process of COVID-19 infection, there is a hypercoagulability condition that is often associated with a poor prognosis. Studies have shown that there are micro and macro level thromboses in various organs, especially in the lungs. Thrombosis is thought to be triggered by a cytokine storm. The most frequently observed thrombotic events during COVID-19 infection are pulmonary embolism (PE) and deep vein thrombosis (DVT).[3] Coagulopathy causes increased mortality in this patients. A significant proportion of patients with severe COVID-19 develop thromboembolic complications, sometimes undetected. In the coexistence of COVID-19 and coagulopathy, the most typical findings are increased d-dimer level, thrombocytopenia and prolongation of prothrombin time.[4] Klok et al. investigated the incidence of symptomatic PE, DVT, myocardial infarction, cerebrovascular accident and arterial embolism in COVID-19 patients and found its cumulative incidence to be 49%. Among all these embolic events, the rate of PE was found to be 89%.[5] In a meta-analysis, in which the data of 102 studies were evaluated, the frequency of COVID-19-related venous thromboembolism (VTE) was 14.7%, and the rates of PE and DVT were 7.8% and 11.2%, respectively. In the same study, the prevalences in the intensive care unit were found to be higher at 23.2%, 29.6% and 11.4%, respectively.[6] Although there is no doubt about the increased incidence of PE in diagnosed patients, there is not enough information in the literature about the tendency to thrombosis in patients with asymptomatic COVID-19 infection. The incidence of PE has increased due to hypercoagulability during COVID-19 infection. A significant part of the population has an asymptomatic infection and they do not receive treatment for COVID-19 and prophylactic treatment for possible thrombosis due to the lack of diagnosis.

In our study, we aimed to investigate whether there is an increase in the frequency of PE in the asymptomatically infected group, in other words, to investigate the underlying cause of asymptomatic COVID-19 infection in patients presenting with PE clinic.

MATERIAL AND METHODS

The study was started after obtaining the approval of the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (date: April 4, 2022, no: 10) and was performed in accordance with the Declaration of Helsinki. It was carried out prospectively. SARS-CoV-2 total spike antibody levels were examined in patients who were diagnosed with PE in the chest diseases department of our hospital but did not have a previous COVID-19 infection and had not vaccinated against COVID-19. The total antibody levels developed against the spike protein were examined in all samples using an Elecsys anti-SARS-CoV-2 S Quantitative (Roche Diagnostics International AG. Rotkreuz Switzerland) kit in accordance with the manufacturer's instructions. A cut-off value of ≥0.8 U/mL was accepted as positive.[7] Demographic data of patients, localization of the thrombus in pulmonary computerized tomography images and reports of the hospital system, whether the thrombus is in a single focus or in multiple focuses, at which level of the pulmonary arteries it is detected, whether there is accompanying DVT in lower extremity doppler ultrasonography, d-dimer, platelet, hemoglobin and hematocrit levels were recorded. In the control group, SARS-CoV-2 total spike antibody levels were examined in patients who applied to our clinic and were not considered to have PE clinically and radiologically, and who had a low Wells score. Antibody titers were recorded in the positive ones. Informed consent was obtained from all patients. Patients who did not give their consent to participate in the study, patients under the age of 18, those who had a previous COVID-19 infection and those who were vacc inated against COVID-19 were excluded from the study.

STATISTICAL ANALYSIS

To determine normal distribution of the continuous variables Kolmogorov-Smirnov test was used. Mean±standard deviation or median (inter quantile range) were used according to normal distribution. Student's t-tests and Mann-Whitney-U test were used for comparison of the data normal distribution or non-

normally distributed, respectively. Chi-squared test was used for the discrete variables.

RESULTS

Thirty two patients were included in the study. Of these, 16 (50%) patients who diagnosed with PE were assigned as the study group, and 16 (50%) patients who followed up with a diagnosis other than PE were assigned as the control group. None of the patients had COVID-19 infection and had not been vaccinated against COVID-19. Of all patients, 22 (68.8%) were male and 10 (31.3%) were female. While the mean age of men was 47.36±14.86 years, the mean age of women was 51±24.463 (p=0.671). In both the study and control groups, 11 (68.8%) of the patients were male and 5 (31.3%) were female. According to the groups, the mean age was 45.44±19.52 in the study group and 51.56±16.52 in the control group, and there was no statistically significant difference between the 2 groups in terms of mean age (p=0.346). When the admission symptoms of both groups were compared, pleuritic chest pain was observed in 50% of the study group, while none of the patients in the control group presented with this complaint. In terms of other symptoms, the 2 groups were statistically similar (Table 1).

None of the patients in the control group had signs of DVT. Venous Doppler USG was performed in only 4 patients in this group, and DVT was not detected in any of them.

While 12 (75%) patients in the study group had risk factors for PE, 6 (37.5%) patients in the control group had risk factors for PE and there was a statistically significant difference between the 2 groups. The mean d-dimer levels and the Wells clinical probability score for PE were found to be statistically significantly higher in the study group (Table 1).

The most common risk factors for PE in all patients were recent surgery, immobilization and presence of malignancy. While 75% (n=12) of the patients in the study group had a risk factor, 31.3% (n=5) of the control group had a known risk factor (Table 2).

When the patient groups were compared in terms of SARS-CoV-2 antibody, antibody positivity was found in 7 (43.8%) patients in both the PE group (study group) and the control group (p=1.000). There was no statistically significant difference between the 2 groups in terms of antibody titers (p=0.275) (Table 3).

TABLE 1: General characteristics of the groups.

	Study group n (%)	Control group n (%)	Total n (%)	p value
Gender				
Male	11 (68.8%)	11 (68.8%)	22 (68.8%)	0.648
Female	5 (31.3%)	5 (31.3%)	10 (31.3%)	
Age	51.56±16.52	45.44±19.52	48.50±18.06	0.346
Symptoms				
Cough	3 (18.8%)	5 (31.3%)	8 (25.0%)	0.685
Dyspnea	5 (31.3%)	10 (62.5%)	15 (46.9%)	0.074
Chest pain	3 (18.8%)	2 (12.5%)	5 (15.6%)	1.000
Pleuritic chest pain	8 (50.0%)	0 (0.0%)	8 (25.0%)	<0.001
Hemoptysis	0 (0.0%)	1 (6.3%)	1 (3.1%)	1.000
Fever	1 (6.3%)	0 (0.0%)	1 (3.1%)	1.000
Muscle-bone pain	1 (6.3%)	1 (6.3%)	2 (6.3%)	1.000
Weakness	1 (6.3%)	1 (6.3%)	2 (6.3%)	1.000
Others	4 (25.0%)	2 (12.5%)	6 (18.8%)	0.654
Other factors				
Risk factors for pulmonary embolism	12 (75.0%)	6 (37.5%)	18 (56.3%)	0.030
D-dimer (ng/mL)	2.45±1.34	10.08±13.25	8.55±12.2	0.038
Wells clinical probability score	2.66±2.15	0.41±0.71	1.53±1.95	0.001

TABLE 2: Pulmonary embolism risk factors.

Pulmonary embolism risk factor	Study group n (%)	Control group n (%)	Total n (%)
Past surgery	5 (31.3%)	0 (0.0%)	5 (15.6%)
Immobilization	3 (18.8%)	2 (12.5%)	5 (15.6%)
Malignancy	4 (25.0%)	3 (18.8%)	7 (21.9%)
No risk factors	4 (25.0%)	11 (68.8%)	15 (46.9%)

TABLE 3: SARS-CoV-2 antibody positivity status and antibody levels.

	Study group n (%)	Control group n (%)	Total n (%)	p value
SARS-CoV-2 total spike antibody positivity	7 (43.8%)	7 (43.8%)	14 (43.8%)	1.000
Antibody titer (U/mL) Median (minimum-maximum)	250.00 (5.05-580.20)	24.98 (4.66-2500.00)	31.4700 (4.66-2500.00)	0.275

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

DISCUSSION

PE prevalence is increased in patients with COVID-19 infection. Although the pathophysiology of this situation has not been fully elucidated, various factors such as vascular endothelial damage and many mediators being released by the cytokine storm thus increasing the release of tissue factor and activating the clotting cascade are suggested.[4] As the severity of COVID-19 increases, PE incidence is also increasing. In a meta-analysis, the incidence of PE was found to be 26% in patients followed in the intensive care unit, 17% in patients hospitalized outside of the intensive care unit, and the cumulative incidence was 21%.[8] For this reason, prophylactic anticoagulant therapy for thromboembolism is recommended in most guidelines in patients with symptomatic COVID-19 who are hospitalized or outpatient. It is emphasized that prophylactic treatment should continue for a while after discharge in patients with risk factors for VTE.[9] However, COVID-19 infection can be undergone with very mild clinic signs or completely asymptomatically. There is no clear data on the risk of thromboembolism and the incidence of PE in this group of patients. Therefore, thromboprophylaxis is not recommended for this group of patients.

Although there is no study on the incidence of PE in asymptomatic COVID-19 patients, when the literature is examined, there are many cases or case series indicating that PE can develop in this group of patients. In the series of 2 patients published by Alharthy et al.; PE was diagnosed 20 and 35 days after polymerase chain reaction (PCR) positivity was detected in asymptomatic 50 and 56 years old female patients who had no previous health problems and positive SARS-CoV-2 PCR test. No thrombophilia or systemic disease was detected in these patients.[10] In another case, on a computerized tomography pulmonary angiography of a 61 yearsold woman who was brought to the emergency department in Rome, Italy due to asudden loss of consciousness and cardiac arrest, a thrombus obstructing the main pulmonary arteries was detected, and this patient had ahistory of contact with COVID-19 patients. 32 days before his death, the SARS-CoV-2 real time (RT)-PCR test was positive.[11] Keane and Dorman investigated the incidence of PE as a cause of death in patients with non-symptomatic COVID-19 and deaths in patients with non-COVID-19. For this purpose, the postmortem reports of the patients were examined and it was determined that the cause of death of 4 cases in the patient group with COVID-19 was PE.[12] In our study, we aimed to reveal whether the underlying asymptomatic COVID-19 infection plays a role in PE patients. The study group and control group were similar in terms of gender and age range. However, most of the patients in the study group had risk factors for PE such as previous surgery, immobilization and malignancy history. COVID-19 infection in the presence of a predisposing factor for PE, although clinically asymptomatic, may have played a facilitating role in the development of thrombosis.

In a case published by Appenzeller et al., factor V Leiden mutation was detectedin a previously healthy 21 years old patient with both deep venous thrombosis and bilateral central PE, as a result of etiological studies. The patient also had a positive SARS-CoV-2 RT-PCR test, although there was no evidence of COVID-19 infection. This situation was interpreted by the authors as that a significant increase in factor V activity in COVID-19 infection may be associated with these thromboembolic events, but it was emphasized that more research is needed for a definitive results.[13]

In our study, the rate of SARS-CoV-2 antibody positivity in patients diagnosed with PE was found to be equal to the control group presenting with other diseases. Although there was no statistically significant difference between the antibody levels, the mean value was higher in the PE group. Considering that asymptomatic patients were followed completely without treatment and no prophylaxis for thrombosis was applied, the results of our study support this decision. The rate of asymptomatic COVID-19 infection in patients with PE is similar to the population followed with non-PE diagnoses.

CONCLUSION

The results of study show that there is no increase in the risk of PE in patients with asymptomatic COVID-19 infection. However, the weakest aspect of our study is that the study was limited to a small group of patients in both groups due to the widespread use of vaccines. Even though the results are within the desirable range, we would like to highlight that further studies are needed in order to make more precise judgements on this subject.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Olcay Ayçiçek;* ***Design:*** *Olcay Ayçiçek, Mehtap Pehlivanlar Küçük;* ***Control/Supervision:*** *Funda Öztuna, Celal Kurtuluş Buruk;* ***Data Collection and/or Processing:*** *Olcay Ayçiçek, Esra Özkaya;* ***Analysis and/or Interpretation:*** *Olcay Ayçiçek, Esra Özkaya;* ***Literature Review:*** *Olcay Ayçiçek, Merve Özdoğan Algın;* ***Writing the Article:*** *Olcay Ayçiçek, Mehtap Pehlivanlar Küçük;* ***Critical Review:*** *Funda Öztuna, Celal Kurtuluş Buruk;* ***References and Fundings:*** *Esra Özkaya.*

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