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Evaluation of the Association between COVID-19 Vaccines and Pulmonary Embolism

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ABSTRACT

Introduction: This study investigated the clinical and radiological characteristics and demographics of patients who developed pulmonary embolism (PE) after Coronavirus disease-2019 (COVID-19) vaccination.

Methods: The cases of PE were analyzed retrospectively. Data on clinical, demographic, and radiologic characteristics, laboratory findings, Pulmonary Embolism Severity Index (PESI) scores, early mortality scores, PE severity classes, and risk categories for early mortality (low-risk, intermediate-high-risk, intermediate-low-risk and high-risk) were collected from patient files as defined in the European Society of Cardiology guidelines. Patients were divided into two groups: those who had received a COVID-19 vaccine (group 1) and those who had not (group 2). Patients who developed PE within 1 month after vaccination were analyzed separately.

Results: A total of 97 patients were included in the study, of whom 61 (62.9%) patients were female. Seventy-five (77.3%) study patients with PE had a history of COVID-19 vaccination (group 1), and 22 (22.7%) had never been vaccinated (group 2). Five (6.6%) patients had received a vaccine within 1 month before PE developed. No significant differences were found between groups 1 and 2 regarding demographics, clinical and radiologic characteristics, laboratory findings, PESI scores, early mortality scores, and PE severity classes ($p>0.05$), except for mean pulmonary artery pressures. The mean age of patients who developed PE within 1 month after vaccination was 74.6 years, and 80% of these patients were female. The average time to PE after vaccination was 22.2 days, and the mean PESI score was 86.6. Two patients (40%) were in the low-risk category for early mortality and one patient (20%) was in the intermediate/high-risk category.

Conclusion: Overall, the characteristics of patients who developed PE after COVID-19 vaccination were comparable to those of patients who had not received a vaccine injection. No statistically significant increases in the incidence of PE were observed within the first month after being vaccinated.

Keywords: COVID-19, COVID-19 vaccine, pulmonary embolism

Introduction

Coronavirus disease-2019 (COVID-19) emerged 4 years ago and was defined as a disease caused by a novel coronavirus strain (2019-nCoV) never previously identified in humans. The disease spread rapidly all over the world and resulted in one of the deadliest pandemics in recent history, mainly transmitted from infected people through droplets generated during activities such as sneezing and coughing. At the beginning of the pandemic, antiviral therapies specific to COVID-19 were not available. In the global pandemic, vaccination is among the most cost-effective ways to fight the disease; therefore, efforts have been made worldwide to develop a vaccine against 2019-nCoV (1,2).

As is well known, vaccine development is a sophisticated process that begins with cell cultures, recombinant DNA technology, and digital modeling to produce strains and antigens to be used in vaccine manufacturing, followed by preclinical studies (phase 0) and clinical trial phases (phase 1, phase 2, and phase 3 clinical trials). As with COVID-19, it may be challenging to develop, perform comprehensive testing, and enable the mass production of effective and, most importantly, reliable vaccines during a pandemic caused by an airborne infection that is rapidly spreading via droplets. Multiple COVID-19 vaccines were developed and approved in a short period and remain in use. However, any vaccine developed and widely administered within a short period should be closely monitored for its effects and possible adverse effects (3-5).

To date, many studies have investigated the effects and adverse effects of COVID-19 vaccines (5-7). Many cases of pulmonary embolism (PE) have been reported in association with COVID-19 vaccination, and studies, mainly consisting of case reports, have suggested a causal relationship

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between COVID-19 vaccination and PE occurring within the first month after vaccination (8,9). This study investigated the clinical, demographic, and radiological characteristics of patients who developed PE after receiving COVID-19 vaccine. Furthermore, subgroup analyses were performed in patients with PE attributed to COVID-19 vaccination who developed PE within the first month after vaccination. The results are reported in light of the literature.

Methods

This retrospective study was designed by the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2023/0768, date: 08.11.2023) and was conducted in line with the principles of the Declaration of Helsinki. Consent was obtained from the patients. Hospital files were retrospectively reviewed to identify patients diagnosed with PE based on computed tomography (CT)-angiography of the chest between August 2021 and September 2023 at the Department of Pulmonary Medicine of our hospital. Data on the clinical, demographic, radiological, and laboratory characteristics of patients were collected from the patient files.

Clinical and demographic characteristics of the study population: For each study patient, age and sex information, comorbidities, body temperature, pulse, blood pressure, and heart rate at diagnosis, as well as oxygen saturation and arterial blood gas, including partial oxygen saturation (pO_2) at hospital admission, were recorded.

Risk factors for pulmonary embolism

The European Society of Cardiology (ESC) Risk factors for PE were recorded for each patient (10).

Major risk factors for PE include hospitalization for lower extremity fractures, heart failure, or atrial fibrillation (last 3 months), hip or knee replacement surgery, major trauma, history of myocardial infarction in the last 3 months, history of venous thromboembolism (VTE), and spinal cord damage.

Intermediate risk factors for PE include arthroscopic knee surgery, autoimmune diseases, blood transfusions, indwelling central venous catheters and intravenous catheters, chemotherapy, congestive heart failure or respiratory failure, erythropoiesis-stimulating agents, hormone replacement therapy, in vitro fertilization, oral contraceptives, postpartum therapy, infections (pneumonia, urinary tract infection and HIV, in particular), inflammatory bowel disease, cancers (higher risk in the presence of metastases), stroke, superficial vein thrombosis, and thrombophilia.

Low-risk factors for PE include bed rest for more than 3 days, diabetes mellitus, elevated arterial blood pressure, prolonged static sitting, advanced age, laparoscopic surgery, obesity, pregnancy, varicose veins, and indwelling venous catheters.

Imaging characteristics of the population: Chest CT angiography findings including the bilateral distribution of thrombi within the pulmonary arterial system, in the root of the pulmonary trunk, lobar, segmental, and subsegmental branches, and any PE-associated infiltrations or pleural effusions were noted. If present, signs of right ventricular strain and pulmonary artery systolic pressure on echocardiogram (ECHO) and any thrombus images on Doppler ultrasound (US) were noted.

Laboratory features of the population: Results from routine laboratory tests, including complete blood counts, white blood cell counts, platelet (PLT) counts, mean platelet volume, C-reactive protein, procalcitonin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, urea and creatinine, electrolytes, troponin, brain natriuretic peptide, D-dimer measurements at diagnosis, and on treatment were reviewed and noted.

Prognostic and early mortality evaluations: The ESC prognostic scores for early mortality were recorded for each patient (10). The Pulmonary Embolism Severity Index (PESI) score was used for the prognostic assessment of PE. According to the guidelines of the ESC, patients were classified as having a low-risk for early mortality in PESI scoring class I and II and high risk for early mortality in PESI scoring class III and above (class III-IV-V) (Supplementary Table 1) (10).

The study patients were classified into low-, intermediate-low-, intermediate-high-, and high-risk groups according to the Classification of Pulmonary Embolism Severity and the risk of early (in-hospital or 30-day) death (Supplementary Table 2). Hemodynamic instability in PE was defined as cardiac arrest, obstructive shock, and persistent hypotension according to the ESC guidelines (Supplementary Table 3) (10).

PESI scores and the numbers of patients in the low-, intermediate-low-, intermediate-high-, intermediate-low-, and high-risk groups for early mortality and, if present, hemodynamic instability were also recorded.

Study patients were divided into two groups based on the presence (group 1) or absence (group 2) of a history of having received any COVID-19 vaccine before the occurrence of PE, and intergroup comparisons were performed. Furthermore, all aforementioned characteristics were documented and analyzed in the subgroup of cases of PE assumed to be related to the vaccine.

The exclusion criteria were uncertainty in the diagnosis of PE or COVID-19, diagnosis of PE using methods other than CT angiography of the chest [e.g. based on ventilation-perfusion (V/Q) scintigraphy, and/or clinical diagnosis], pregnancy, and age under 18 years.

Statistical Analysis

All data were analyzed using SPSS 17.0 software (IBM Inc. Released in 2008. SPSS Statistics for Windows (Chicago, USA). In descriptive statistics, normally distributed continuous variables are presented as means ± standard deviation, and categorical variables are presented as percentages. The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. The chi-square and Mann-Whitney U tests were used for intergroup comparisons of data. A p-value of less than 0.05 was considered significant.

Results

In total, 130 patient files were reviewed for eligibility. Out of the 130 patients, 30 were excluded because their vaccination status was unknown, two were excluded because of uncertainty regarding the diagnosis of COVID-19, and one was excluded because the diagnosis of PE was made based on V/Q scintigraphy (Figure 1).

The mean age of the overall study patients was 67.7±18 years, a total of 97 patients, including 61 (62.9%) females and 36 (37.1%) males were found to be eligible for the study. Seventy-five study patients had a history of COVID-19 vaccination before the diagnosis of PE (group 1), whereas 22 study patients (22.7%) had not (group 2). The mean time to the diagnosis of PE after getting vaccinated against COVID-19 was 227.3±157.7 days (minimum-maximum: 9 days and 793 days, respectively) in group 1. Five (6.6%) study patients were diagnosed with PE within 1 month after being vaccinated, and eight (10.6%) study patients were diagnosed with PE at month 2 after being vaccinated (Figure 2). Fifty-two patients received nucleic acid vaccines-COVID-19 vaccines (mRNA) and 23 patients (30.7%) received inactivated vaccines.

Regarding the risk factors for PE, 47 (62.7%) patients in group 1 and 14 (63.7%) patients in group 2 had one risk factor for developing PE (p=0.934). Thirty-four (45.3%) patients in group 1 and six (27.2%) patients in group 2 had major or intermediate risk factors (0.130). Eleven patients in group 1 (14.6%) and eight patients (36.6%) had a low-risk factor (0.034) (Table 1).

Seventy-three (75.3%) patients had a comorbidity and 24 patients (24.7%) did not. Hypertension (HTN) was the most common comorbidity in 37 patients. The mean length of hospital stay was 9.47±5.65 days [9.45±5.2 days in groups 1 and 9.55±6.9 days in group 2 (p=0.431)]. The clinical and demographic characteristics of the study patients are presented in Table 2, and the laboratory test results are presented in Table 3. Based on echocardiographic measurements, the PABs were 46.1±11.5 in patients who had received a COVID-19 vaccination and 38.3±15.9 in those who had not (p=0.022). No other intergroup statistically significant differences were found in other radiologic variables. Data from comprehensive imaging studies (CT-angiography of the chest, ECHO, bilateral lower extremity venous Doppler US) are presented in Table 4.

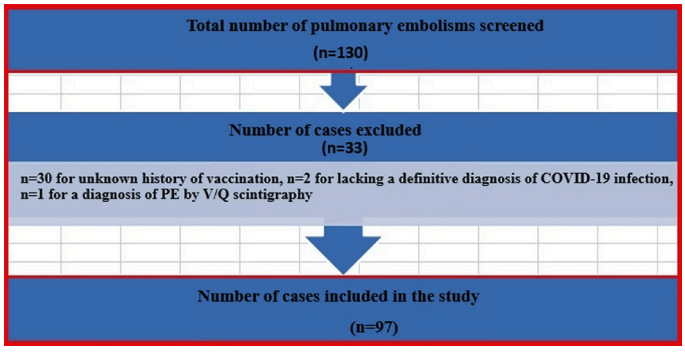

Figure 1. Flow chart
COVID-19: Coronavirus disease-2019, PE: Pulmonary embolism

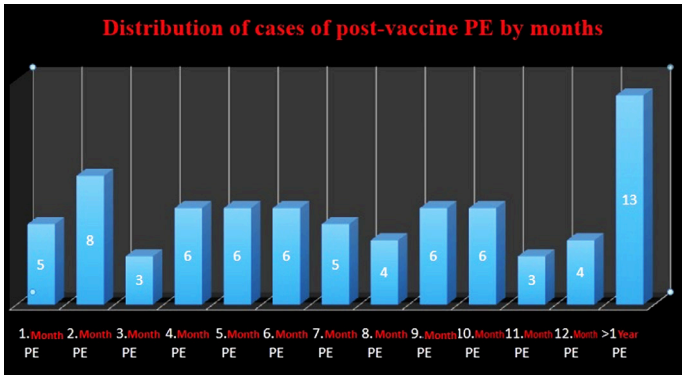

Figure 2. Distribution of cases of post-vaccine PE according to months
PE: Pulmonary embolism

Table 1. Distribution of study patients according to risk factors

	COVID-19 vaccinated (group 1; n=75)	COVID-19 unvaccinated (group 2; n=22)	p-value
Major risk factors (n, %)	22-29.3%	3-13.6%	0.139
Intermediate-risk factors (n, %)	12-16%	3-13.6%	1
Low-risk factors (n, %)	11-14.6%	8-36.3%	**0.034**
Inherited risk factors (n, %)	2-2.6%	-	1
No risk factors (n, %)	28-37.3%	8-36.3%	0.934

COVID-19: Coronavirus disease-2019

Table 2. Patient demographics and clinical characteristics of patients

	COVID-19 vaccinated (group 1; n=75)	COVID-19 unvaccinated (group 2; n=22)	p-value
Age (mean ± SD)	66.5±18.4	71.7±16.3	0.199
Sex (F/M; n, %)	47-62.6/28-37.4%	14-63.6/8-36.3%	0.934
Hospital stay (days, mean ± SD)	9.45±5.2	9.55±6.9	0.431
Comorbidities			
- Any comorbidity (n, %)	56-74.6%	17-77.2%	0.803
- Hypertension (n, %)	30-40%	7-31.8%	0.487
- Malignancy	16-21.3%	2-9%	0.348
- DM (n, %)	16-21.3%	5-22.7%	1
- CAD (n, %)	9-12%	2-9%	1
- CHF (n, %)	6-8%	2-9%	1
- COPD (n, %)	9-12%	2-9%	1
- Asthma (n, %)	4-5.3%	1-4.5%	1
- CVA (n, %)	7-9.3%	2-9%	1
- CKF (n, %)	2-2.6%	0-	1
Body temperature (mean ± SD) (°C)	36.5±0.2	36.4±0.1	0.222
Heart rate (mean ± SD) (/minute)	94.7±19	95.9±21	0.919
Systolic blood pressure (mean ± SD) (mmHg)	127.6±26.1	116.3±21.4	0.095
Diastolic blood pressure (mean ± SD) (mmHg)	74.6±12.7	68±13.1	0.070
Admission oxygen saturation (%)	90.3±4.5	91.7±4.2	0.197
ABG-pO^2 (mmHg) (mean ± SD)	60.3±13.2	63.5±14.5	0.274

ABG: Arterial blood gas, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CAD: Coronary arterial disease, CKF: Chronic kidney failure, mmHg: millimeter mercury, pO_2: Partial oxygen pressure, SD: Standard deviation, CVA: Cerebrovascular accident

The mean PESI score was 99.9±33.5 in group 1 and 104±38.9 in group 2 (p=0.763). Fifty-one patients (68%) in group 1 were classified as PESI-III or higher, and 13 patients (59%) were classified as PESI-III or higher in group 2 (p=0.438) (Table 5). The assessment of the risk of early death revealed that 10 patients (13.3%) in group 1 and two patients (9%) in group 2 were at high risk of early mortality (p=0.729). Nine (12%) patients and two (9%) patients presented with hemodynamic instability in groups 1 and 2, respectively (p=1). No statistically significant intergroup differences were observed regarding prognostic status and early mortality scores (Table 6).

Subgroup analyses of PE cases attributable to vaccination: Five patients in group 1 were diagnosed with PE within 1 month after being vaccinated against COVID-19. The mean age of these patients was 74.6±19.4 (minimum: 43, maximum: 92) years, and four (80%) patients were women. The mean time interval between getting vaccinated and PE onset was 22.2±10.1 (minimum: 9, maximum: 31) days. Among these patients, two (40%) received an inactive vaccine and three (60%) received an mRNA vaccine before developing PE. No risk factors were detected in three patients (60%); one patient (20%) had a low-risk factor, and one patient (20%) had an inherited risk factor for PE. Comorbidities were identified in four patients (80%), and one patient (20%) had no comorbidities. The most prevalent comorbidity was HTN (n=3, 60%). The mean length of hospital stay was 5.6±0.8 (minimum: 5, maximum: 7) days. The mean PLT count was 273,400±142,449 (minimum: 126,000, maximum: 440,000). Imaging studies revealed that PE mostly affected the bilateral subsegmental branches of pulmonary arteries (three patients, 60%) (Table 7). The mean PESI score was 86.6±16.7.

Table 3. Laboratory characteristics

	COVID-19 vaccinated (group 1; n=75)	COVID-19 unvaccinated (group 2; n=22)	p-value
Laboratory parameters			
WBC (mean ± SD) (/uL)	10,934±4,203	8,981±3,432	0.189
Hb (mean ± SD) (g/dL)	12.1±2	12.1±2.1	0.911
PLT (mean ± SD) (/uL)	244,733±88,415	278,272±124,129	0.268
MPV (mean ± SD) (/uL)	10.8±1.4	10.2±0.9	0.245
LDH (mean ± SD) (U/L)	285.8±174.9	236.7±127.5	0.338
D-dimer level (mean ± SD) (mg/L)	10.5±9.8	12±10.9	0.619
Urea (mean ± SD) (mg/dL)	50.3±58.1	40.2±12.1	0.850
Creatinine (mean ± SD) (mg/dL)	1±0.5	0.77±0.2	0.011
ALT (mean ± SD) (U/L)	31.4±39	21.2±20.2	0.110
AST (mean ± SD) (U/L)	34.7±39.5	24.8±17.8	0.144
Albumin (mean ± SD) (g/L)	36.5±5.9	36±6.5	0.945
BNP (mean ± SD) (ng/L)	3674±6044	4119±4809	0.336
Troponin (mean ± SD) (ng/L)	77±145.8	77.3±144.4	0.181

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BNP: Brain natriuretic peptide, CRP: C-reactive protein, HB: Hemoglobin, LDH: Lactate dehydrogenase, MPV: Mean platelet volume, PLT: Platelet, PRC: Procalcitonin, SD: Standard deviation, WBC: White blood cell

Table 4. Imaging and echocardiographic characteristics

	COVID-19 vaccinated (group 1; n=75)	COVID-19 unvaccinated (group 2; n=22)	p-value
Embolism in the main pulmonary artery (n, %)	1-1.3%	0	1
Embolism in the left pulmonary artery (n, %)	11-14.6%	5-22.7%	0.350
Embolism in the right pulmonary artery (n, %)	4-5.3%	2-9%	0.616
Embolism in both pulmonary arteries (n, %)	18-24%	6-27.2%	0.754
Embolism in unilateral segmental branches (n, %)	26-34.6%	2-9%	0.020
Embolism in bilateral segmental branches (n, %)	40-53.3%	13-59%	0.613
Embolism in unilateral subsegmental branches (n, %)	23-30.6%	2-9%	0.042
Embolism in bilateral subsegmental branches (n, %)	41-54.6%	12-54.5%	0.992
Pleural effusion associated with pulmonary embolism (n, %)	17-22.6%	9-40.9%	0.089
Parenchymal infarct area (n, %)	37-49.3%	11-50%	0.956
Thrombus on Doppler US (n, %)	18-24%	8-36.3%	0.250
Right ventricular involvement in ECHO (n, %)	28-37.3%	12-54.5%	0.149
PAP value on ECHO (mean ± SD) (mmHg)	38.3±15.9	46.1±11.5	0.022

ECHO: Echocardiogram, PAPs: Systolic pulmonary arterial pressure, mmHg: Millimeter mercury, US: Ultrasound, COVID-19: Coronavirus disease-2019

Table 5. Patient distribution according to PESI scores

	COVID-19 vaccinated (group 1; n=75)	COVID-19 unvaccinated (group 2; n=22)	p-value
PESI-I (n, %)	11-15.3%	2-12.6%	0.726
PESI-II (n, %)	13-17.3%	7-26.2%	0.147
PESI-III (n, %)	19-26.9%	3-24.2%	0.386
PESI-IV (n, %)	18-30.7%	3-21.3%	0.387
PESI-V (n, %)	14-26.9%	7-15.5%	0.239

PESI: Pulmonary Embolism Severity Index, COVID-19: Coronavirus disease-2019

Tablo 6. Patient distribution by EMA

	COVID-19 vaccinated (group 1; n=75)	COVID-19 unvaccinated (group 2; n=22)	p-value
High	10-13.3%	2-9%	0.729
Intermediate-high	15-20%	2-9%	0.344
Intermediate-low	26-34.6%	7-31.8%	0.804
Low	24-32%	11-50%	0.122

EMA: Early mortality assessment [classification of pulmonary embolism severity and the risk of early death (in-hospital or 30-day)]

Table 7. Demographics, clinical, laboratory, and radiological characteristics of patients with PE attributable to vaccine

	Patients who developed PE within the first month after receiving COVID-19 vaccine (n=5)
Age (mean ± SD)	74.6±19.4
Sex (F/M; n, %)	4-8/1-20%
Comorbidities	
- Hypertension (n, %)	3-60%
- CAD (n, %)	1-20%
- COPD (n, %)	1-20%
- Hypothyroidism (n, %)	1-20%
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- Body temperature (mean ± SD)	36.4±0.22
- Heart rate (mean ± SD)	101±20.7
- Systolic blood pressure (mean ± SD)	119±7.4
- Diastolic blood pressure (mean ± SD)	71.6±13.5
- Admission oxygen saturation (mean, %)	91.8±2.8
- ABG-pO_2 (mmHg) (mean ± SD)	58±3.2
Laboratory parameters	
- WBC (mean ± SD) (/uL)	10,880±7,143
- Hb (mean ± SD) (g/dL)	13.2±2.2
- PLT (mean ± SD) (/uL)	273,400±142,449
- LDH (mean ± SD) (U/L)	257.4±148.7
- D-Dimer level (mean ± SD) (mg/L)	12.9±13.2
- Urea (mean ± SD) (mg/dL)	44.2±15.2
- Creatinine (mean ± SD) (mg/dL)	0.94±0.48
- BNP (mean ± SD) (ng/L)	379±298.9
- Troponin (mean ± SD) (ng/L)	45.7±57.5
Imaging parameters	
- Embolism in the left pulmonary artery (n, %)	1-20%
- Embolism in the right pulmonary artery (n, %)	1-20%
- Embolism in both pulmonary arteries (n, %)	1-20%
- Embolism in unilateral segmental branches (n, %)	2-40%
- Embolism in bilateral segmental branches (n, %)	2-40%
- Embolism in unilateral subsegmental branches (n, %)	2-40%
- Embolism in bilateral subsegmental branches (n, %)	3-60%
- Pleural effusion associated with pulmonary embolism (n, %)	2-40%
- Parenchymal infarct area (n, %)	2-40%
- Thrombus on Doppler US (n, %)	2-40%
- Right ventricular involvement in ECHO (n, %)	2-40%
- PAP value on ECHO (mean ± SD) (mmHg)	51.6±23.6

ABG: Arterial blood gas, BNP: Brain natriuretic peptide, ECHO, Echocardiogram, Hb, hemoglobin, COPD: Chronic obstructive pulmonary disease, CAD: Coronary arterial disease, LDH: Lactate dehydrogenase, mmHg: Millimeter mercury, PAPs: Systolic pulmonary arterial pressure, pO_2: Partial oxygen pressure, SD: Standard deviation, US: Ultrasound, WBC: White Blood Cell

One patient was classified into PESI class 1, one patient was classified into PESI class II, two patients were classified into PESI class III, and one patient was classified into PESI class IV, indicating that the PESI class was III or higher in three (60%) patients. Two (40%) patients were at low-risk, two patients (40%) were in the intermediate-low-risk group, and one patient (20%) was classified into the intermediate/high-risk group. No patients were hemodynamically unstable.

Discussion

This study investigated the features of patients diagnosed with PE after being vaccinated against COVID-19. The rate of patients with PE within 1 month after being vaccinated was 6.6% in the overall study population. No significant differences were found between the group of patients who received COVID-19 vaccine before being diagnosed with PE and the group of patients who did not have clinical, radiological, or laboratory characteristics. The assessment of the presence of risk factors for PE revealed no intergroup differences in risk factors (p=0.934). As an interesting finding, low-risk factors were significantly less prevalent in group 1 (p=0.034).

At the time of writing this article, the total number of COVID-19 vaccine doses administered was 152 million in our country and approximately 1.5 billion in Europe (11,12). The COVID-19 pandemic has accelerated efforts to develop vaccines and build an extensive vaccination program worldwide. Upon the initiation of vaccination programs, several adverse effects have been reported in association with these rapidly developed and widely used vaccines. Increased incidences of thrombotic events, including DIC, cerebral venous sinus thrombosis, hemorrhagic stroke, and PE, were reported from a study in a population of 5.5 million individuals, particularly those vaccinated with ChAdOx1 nCoV-19, AZD1222, a recombinant adenovirus vaccine encoding the SARS-CoV-2 spike glycoprotein. These events predominantly occurred in women aged 60 years, and thrombocytopenia was documented in most thrombotic events. These patients usually deteriorate 6-12 days after being vaccinated (13,14). Increased risk for PE (out of 54,571 adverse events, there were 28 cases of PE and four deaths) after AZD1222 vaccination, and the decision for temporary suspension of the use of the vaccine suggested an association between this vaccine and PE (15).

In one of the limited retrospective studies on this association, Scully et al. (16) analyzed data from 23 patients who presented with thrombosis and thrombocytopenia 6-24 days after receiving COVID-19 vaccine injection. In their study, five out of 23 patients were diagnosed with PE, and 22 tested positive for platelet factor 4. The mean age was 44 years, 60% of the patients were female, and the mean PLT count was 43,200. In our study, the mean age was 66 years in the post-vaccine PE group (62% were female, and the mean PLT count was 244,733. Among those diagnosed with PE within 1 month (5 patients), the mean age was 74.6 years, 80% were female, and the mean PLT count was 273,400 after vaccination. Our results were not consistent with the literature regarding patient characteristics, except for sex.

In the literature, cases of post-vaccine PE are usually reported as case reports. An analysis of 10 recently published cases indicated that the mean patient age was 57 years, 80% were male, and all patients developed PE after receiving a live vaccine injection (100%). The mean

PESI score was 94.5 (minimum: 41, maximum: 129), and the distribution of patients according to the PESI classes was as follows: PESI class 1, 20%; PESI class 2, 10%; PESI class 3, 30%; PESI class 4, 20%; and PESI class 5, 20%. Twenty percent of patients were at high risk, 20% were intermediate high risk, 30% were intermediate-low-risk, and 30% were low-risk for early mortality (9,17-25) (Figure 3). In our study, the mean age was 74 years, and 80% of the patients were female in the group of patients who developed PE after being vaccinated. Sixty percent of patients received a live mRNA vaccine. The mean PESI score was 104, and 15.3% were classified as PESI class 1, 17.3% were PESI class 2, 26.9% were PESI class 3, 39.7% were PESI class 4, and 26.9% were classified as PESI class 5. By contrast, for the early mortality assessment, 13.3% of patients were at high risk, 20% were intermediate high, 34.6% were intermediate/low-risk, and 32% were at low-risk (Figure 4).

Recently, adverse effects associated with COVID-19 mRNA vaccines were investigated by Yasmin et al. (26) in a meta-analysis that included a total of 81 articles and 17,636 patients, and the most common adverse effects were thrombosis (n=3936), CVH (n=758), myocarditis (n=511), myocardial infarction (n=377), PE (n=301), and arrhythmias (n=254). Although PE is a relatively uncommon complication, the authors stated that PE might increase mortality along with myocarditis. Similarly, Favas et al. (27) conducted a meta-analysis that included 59 articles, 202 patients, and 306 events to investigate post-vaccine thrombotic and thromboembolic complications. They reported that 74.8% of patients experienced VTE events, 12.7% developed arterial thromboembolic events, and the remaining developed hemorrhagic complications. PE was reported in 17.8%. The mean patient age was 47 years, 71% of patients were female, the time to event was 14 days (minimum: 1 day and maximum: 37 days), and almost all vaccines associated with events were live/mRNA vaccines. Our study was in line with the literature based on these results. Finally, Wong et al. (28) investigated vaccine safety in patients aged ≥65 years who received 17 million doses and detected remarkable increases in the incidences of PE, myocardial infarction, disseminated intravascular coagulopathy, and immune thrombocytopenia, although only PE was statistically significantly associated with COVID-19 vaccination after the adjustments. The largest amount of information about COVID-19 vaccines and PE available in the English medical literature is from studies involving live/mRNA vaccines. In a postmortem study involving inactive vaccines, Chaves et al. (29) found that 118 out of 121 (97.52%) deceased patients had been vaccinated with an inactive vaccine, and PE was the second most common cause of death (n=25, 20.66%) after sudden cardiac death. In our study, 30% of patients experiencing post-vaccine PE received an inactive vaccine. Inactive vaccines accounted for 40% of the to date, studies and case reports have mostly underlined the hypothesis that COVID-19 vaccines might increase the incidence of PE. However, Tantillo et al. (30) made a very different assumption that had never been investigated before; they investigated whether COVID-19 vaccines could prevent PE. Surprisingly, they found that PE was significantly more prevalent among patients who had NOT received a COVID-19 vaccine. The authors further explained their assumptions using citations from a study conducted by Agrati et al. (31): "We can just hypothesize a possible protective role of vaccination through action on the immune system, modulating the inflammation-coagulation interface".

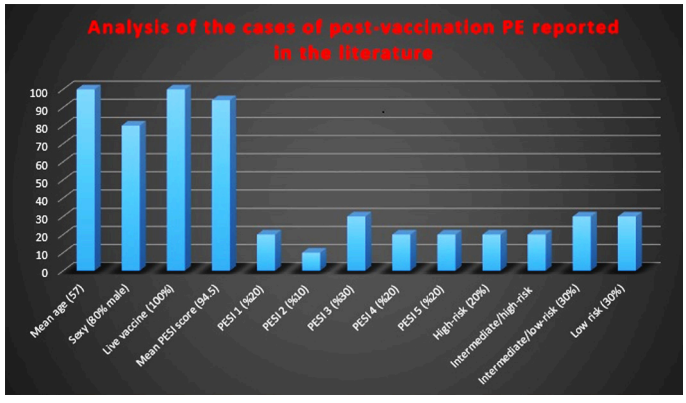

Figure 3. Analysis of postvaccination PE cases reported in the literature
PE: Pulmonary embolism, PESI: Pulmonary Embolism Severity Index

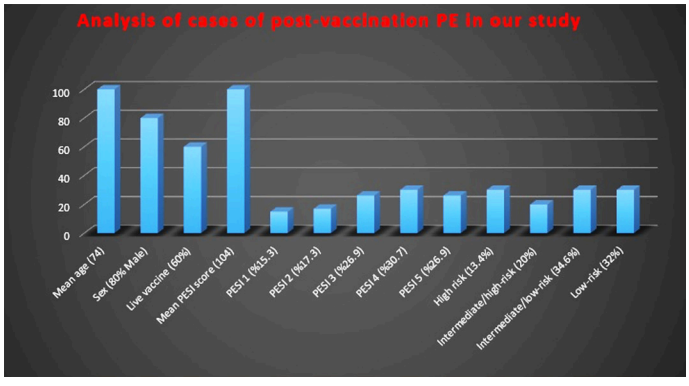

Figure 4. Analysis of postvaccination PE cases in our study
PE: Pulmonary embolism, PESI: Pulmonary Embolism Severity Index

Study Limitations

The present study has some limitations that should be considered when interpreting the results. This study has a retrospective design and reflects a single-site experience. Therefore, the results cannot be generalized. Furthermore, the small sample size, particularly the very limited number of PE cases attributed to vaccines, did not provide sufficient power for statistical analysis. The limited number of cases can be explained by the relatively low incidence of PE. Future studies should have a multicenter design to overcome this limitation.

Many studies have demonstrated several adverse effects associated with COVID-19 vaccination. Moreover, the speed of the development of COVID-19 vaccines has been the primary concern in these studies (32). Therefore, healthcare professionals from branches/disciplines involved in COVID-19 should enhance their knowledge and better manage the effects and adverse effects of vaccines.

Conclusion

In conclusion, the present study analyzed cases of PE after COVID-19 vaccination. Regarding vaccine complications reported in the medical literature, PE was a relatively less common complication in most studies. However, several studies have suggested that COVID-19 vaccines might decrease the incidence of PE. The parameters analyzed in our study and the results are not sufficient to achieve definitive conclusions on whether COVID-19 vaccines increase or decrease the incidence of PE;

however, considering the number of cases of PE during the first 12 months after vaccination, the cases were not significantly clustered nor did they increase in the first month [month 1, (n=5); month 2, (n=8); month 3, (n=3); month 4, month 5, (n=6); month 6, (n=6) cases (Figure 2)]. Independent of the results, we believe that the potential benefits of COVID-19 vaccines outweigh the potential risks of a COVID-19 infection.

Ethics Committee Approval: This retrospective study was designed by the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2023/0768, date: 08.11.2023) and was conducted in line with the principles of the Declaration of Helsinki.

Informed Consent: Consent was obtained from the patients.

Authorship Contributions: Surgical and Medical Practices - C.D., S.S.; Concept - C.D.; Design - C.D.; Data Collection or Processing - S.S.; Analysis or Interpretation - C.D.; Literature Search - S.S.; Writing - C.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Table 1. PESI scoring scores

Variable	PESI	
>80 years of age	Age/years	
Male sex	+10 points	
History of cancer	+30 points	
History of heart failure	+10 points	
History of chronic lung disease	+10 points	
Heart rate ≥110/bpm	+20 points	
Systolic blood pressure <100 mm Hg	+30 points	
Respiratory rate ≥30/minute	+20 points	
Body temperature <36 °C	+20 points	
Altered mental health	+60 points	
SpO_2 <90%	+20 points	
	Low-risk Class I: ≤65 Class II: 66-85	**High-risk** Class III: 86-105 Class IV: 106-125 Class V: >125

PESI: Pulmonary Embolism Severity Index

Supplementary Table 2. Classification of pulmonary embolism severity and the risk of early death

		Risk indicators		
Early mortality risk	**Hemodynamic instability**	**PESI class III-IV**	**Ventricular dysfunction on TTE or computed tomography angiography**	**Increased cardiac troponin levels**
High	+	+	+	+
Intermediate-high	-	+	+	+
Intermediate-low	-	+	One (+) or both (-)	
Low	-	-	-	-

PESI: Pulmonary Embolism Severity Index, TTE: Transthoracic echocardiography

Supplementary Table 3. Definition of hemodynamic instability in pulmonary embolism

Cardiac arrest	Obstructive shock	Persistent hypotension
Cardiac arrest necessitates cardiopulmonary resuscitation	Systolic blood pressure of <90 mmHg or Need for a vasopressor to maintain systolic blood pressure at ≥90 mmHg despite adequate fluid replacement and End organ hypoperfusion (altered mental status, cold and clammy skin, oliguria/anuria, increased serum lactate levels)	Systolic blood pressure of <90 mmHg or Systolic blood pressure decrease of more than 40 mmHg (New-onset arrythmia lasting longer than 15 minutes, that cannot be explained by hypovolemia or sepsis)