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Incidence of Pulmonary Vascular Thrombosis in Intensive Care Units Following COVID-19 Vaccination

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A B S T R A C T

Introduction: While COVID-19 vaccines substantially reduced global mortality, rare hypercoagulable safety signals such as immunothrombosis emerged. In critically ill ICU patients, pre-existing systemic inflammation and endothelial strain may compound these thrombotic risks within the delicate pulmonary vasculature. Consequently, this study aimed to evaluate the incidence and clinical characteristics of pulmonary vascular thrombosis in ICU patients following COVID-19 vaccination.

Material and methods: This cross-sectional study was conducted at Imam Reza Center, Tabriz, recruiting 250 ICU patients selected via convenience sampling based on Cochran's formula. Eligible post-vaccination patients were evaluated for pulmonary vascular thrombosis using CTPA. Demographic, clinical, hemodynamic, and laboratory data including D-dimer and anti-PF4 levels were abstracted from medical records and analyzed to identify clinical predictors.

Results: Pulmonary vascular thrombosis significantly correlated with thrombocytopenia (61.8% vs. 17.6%, P<0.001), elevated D-dimer (6.84±3.42 vs. 2.22±1.28 mg/L FEU, P<0.001), and higher mPAP (31.40±8.24 vs. 22.33±4.98 mmHg, P<0.001). Multivariable regression identified anti-PF4 positivity (aOR:6.842, 95% CI:2.418–19.362, P<0.001), thrombocytopenia (aOR:3.428, 95% CI:1.584-7.418, P=0.002), and adenoviral vaccination (aOR:2.815, 95% CI:1.382-5.735, P=0.004) as independent predictors.

Conclusion: Post-vaccination pulmonary vascular thrombosis in critically ill patients is independently driven by adenoviral vector platforms, thrombocytopenia, and anti-PF4 seropositivity, leading to marked hemodynamic compromise. Routine screening with D-dimer, platelet counts, and anti-PF4 antibody assays facilitates early risk stratification, timely intervention, and mitigated ICU mortality.

Introduction

The emergence of the COVID-19 pandemic necessitated a global scientific mobilization of unprecedented scale, culminating in the rapid development and deployment of various vaccine platforms to mitigate morbidity and mortality. These vaccination campaigns have undoubtedly averted millions of deaths and hospitalizations, significantly altering the trajectory of the pandemic. However, as administration reached global coverage, the medical community observed rare but severe adverse events that warranted intensive pharmacovigilance. Among these, thrombotic complications, particularly those involving the venous system and paradoxical

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thrombotic thrombocytopenia, emerged as a significant safety signal, particularly regarding adenoviral vector-based vaccines. As the scientific community continues to refine its understanding of the immunogenicity of these vaccines, there remains a critical imperative to delineate the interplay between vaccination-induced immune responses and the hypercoagulable states prevalent in critically ill populations [1].

The underlying pathophysiology linking specific vaccine platforms to thrombotic events has been extensively studied, with particular attention directed toward Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). This syndrome shares mechanistic similarities with heparin-induced thrombocytopenia (HIT), wherein the immune system generates antibodies against platelet factor 4 (PF4), leading to massive platelet activation and subsequent thrombosis in unusual anatomical sites. While the majority of vaccination efforts have maintained a highly favorable safety profile, the theoretical risk of such aberrant immune activation poses unique challenges, especially when considering the complex coagulopathic milieu of patients already admitted to intensive care units (ICUs) for respiratory failure or multi-organ dysfunction. Understanding whether vaccination status exacerbates these inherent risks or introduces a new etiology of pulmonary vascular thrombosis is essential for refining clinical protocols and ensuring patient safety in the most vulnerable cohorts [2].

Pulmonary vascular thrombosis in the critically ill represents a particularly lethal complication, often exacerbated by the systemic inflammatory environment characteristic of severe COVID-19. The pulmonary vasculature serves as a primary interface for gas exchange and is highly sensitive to immunologic insult and endothelial cell activation. During the course of severe viral infections, the activation of the coagulation cascade often termed "immunothrombosis" is a well-documented phenomenon. When vaccination, which is designed to elicit a robust immune response, is introduced into this clinical picture, the potential for additive effects on endothelial integrity and vascular resistance must be rigorously evaluated. The pulmonary artery, in particular, is subject to high flow and shear stress, rendering it susceptible to the formation of thrombi, especially if the endothelial glycocalyx is already compromised by viral or inflammatory factors [3].

Critically ill patients in the ICU represent a population defined by a profound pro-thrombotic state. Whether due to prolonged immobilization, the presence of central venous catheters, or the systemic inflammatory response syndrome (SIRS), these patients are perpetually at risk for venous thromboembolism (VTE). Distinguishing between thromboembolic events arising from the natural disease progression of COVID-19 or other critical illnesses and those that may be temporally related to recent vaccination is a complex clinical puzzle. The high mortality rate associated with acute pulmonary vascular thrombosis necessitates an objective analysis of whether vaccination status independently contributes to the incidence, severity, or clinical phenotype of these events in the ICU setting. This differentiation is paramount for both diagnostic accuracy and the implementation of appropriate prophylactic anticoagulation strategies [4].

Despite the growing body of literature concerning vaccine safety, current evidence regarding pulmonary vascular thrombosis specifically in the ICU setting remains fragmented and primarily confined to case series or retrospective observational studies with limited power. Many existing studies have focused on the general population or hospital-wide cohorts, failing to isolate the specific physiological vulnerability of the critically ill patient. This creates a substantial gap in clinical knowledge, leaving intensivists to rely on general guidelines that may not fully account for the unique synergy between post-vaccination immune activity and the "cytokine storm" of critical illness. Without robust, specialized data, clinicians face uncertainty in navigating the risks and benefits of prophylactic measures, potentially leading to undertreatment or, conversely, unnecessary diagnostic intervention [5].

Therefore, to address this critical knowledge deficit and provide evidence-based guidance for the management of the most vulnerable patient populations, this study aims to evaluate the incidence and clinical characteristics of pulmonary vascular thrombosis among patients admitted to intensive care units, specifically analyzing the temporal and pathophysiological associations following COVID-19 vaccination.

Material and methods

Study Design and Setting

This study was conducted using a cross-sectional descriptive design at Imam Reza Educational and Medical Center, a major tertiary referral heart and vascular hospital affiliated with Tabriz University of Medical Sciences, Tabriz, Iran.

Sample Size and Sampling Technique

The required sample size was calculated using Cochran's formula for estimating a population proportion, assuming a 95% confidence interval (α=0.05), a margin of error (d) of 0.05, and an estimated prevalence (p) based on initial pilot observations in the ICU setting. Consequently, the minimum statistical sample size was determined to be 250 patients. Participants were selected using a non-probability convenience sampling technique from consecutive admissions to the intensive care units who met the predefined eligibility criteria.

Inclusion and Exclusion Criteria

The inclusion criteria mandated adult patients aged 18 years or older admitted to the ICU who had received at least one dose of a authorized COVID-19 vaccine (including vector-based or inactivated platforms) within 42 days prior to ICU admission, and who provided informed consent (or via their legally authorized representative). Additionally, eligibility required definitive imaging confirmation of acute pulmonary vascular thrombosis via Contrast-Enhanced Computed Tomography Pulmonary Angiography (CTPA) or high-probability Ventilation-Perfusion (V/Q) SPECT scanning performed during the ICU stay. Exclusion criteria comprised patients with a prior documented history of venous thromboembolism (VTE), pulmonary embolism, or confirmed active pulmonary hypertension prior to vaccination; known underlying severe inherited or acquired thrombophilia (such as Factor V Leiden, Antithrombin III deficiency, or Antiphospholipid Syndrome); active malignancy under systemic therapy; history of heparin-induced thrombocytopenia (HIT); patients transferred from external facilities without verified pre-admission documentation; and individuals with an ICU stay of less than 24 hours due to immediate mortality or discharge.

Data Collection and Operational Procedures

Data collection was systematically conducted through structured medical record abstraction and clinical assessment protocols upon ICU admission and throughout the hospitalization period. Demographic characteristics recorded included patient age, biological sex, body mass index (BMI), smoking status, and primary reason for ICU admission. Clinical variables encompassed the specific COVID-19 vaccine platform administered (adenoviral vector vs. inactivated virus), number of vaccine doses, exact time interval between the last vaccination dose and symptom onset/ICU admission, acute physiology and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA) score, mechanical ventilation requirements, and duration of ICU stay.

Furthermore, detailed physiological and biochemical parameters were systematically recorded at the time of confirmed thrombosis diagnosis. Respiratory and hemodynamic metrics included partial pressure of arterial oxygen to fractional inspired oxygen ratio (PaO2/FiO2), peripheral oxygen saturation (SpO2), pulmonary artery systolic pressure (PASP), and mean pulmonary artery pressure (mPAP) measured via Doppler echocardiography or invasive pulmonary catheterization. Complete laboratory evaluations comprised full blood counts (specifically platelet counts to screen for VITT), prothrombin time (PT), activated partial thromboplastin time (aPTT), quantitative D-dimer, C-reactive protein (CRP), serum ferritin, fibrinogen levels, and anti-Platelet Factor 4 (anti-PF4) antibody titers when clinically indicated.

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 26.0, IBM Corp., Armonk, NY, USA). Continuous variables were subjected to the Shapiro-Wilk test to assess the normality of data distribution. As the parametric assumptions were met, continuous data were presented as mean ± standard deviation (SD), whereas categorical variables were reported as absolute counts and percentages. Differences between patient subgroups (e.g., vaccine platforms or survival outcomes) were analyzed using the independent samples Student's t-test for continuous parametric variables, and the Pearson Chi-square test or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was conducted to identify independent predictor variables associated with acute pulmonary vascular thrombosis, reporting adjusted Odds Ratios (OR) with corresponding 95% Confidence Intervals (CI). A two-tailed p-value of less than 0.05 was considered statistically significant for all tests.

Ethical Considerations

The protocol of this research was reviewed, approved, and granted formal ethical clearance by the Regional Ethics Committee of Tabriz University of Medical Sciences under the registration ethics code IR.TBZMED.REC.1400.1091. Written informed consent was obtained from all patients or their legal surrogates prior to inclusion, strictly adhering to the ethical principles of the Declaration of Helsinki and maintaining complete patient data.

Results

As detailed in Table 1, patients who developed pulmonary vascular thrombosis exhibited significantly higher disease severity upon ICU admission, reflected by elevated APACHE II (19.45 ± 5.68 vs. 15.84 ± 4.89, P<0.001) and SOFA scores (7.85 ± 2.64 vs. 5.88 ± 2.26, P<0.001) compared to their non-thrombotic counterparts. Individuals receiving adenoviral vector-based vaccines demonstrated a substantially higher incidence of thrombosis than those immunized with inactivated viral platforms (57.4% vs. 42.6%, P=0.001), with a significantly shorter time interval between the last vaccine administration and ICU admission (13.82 ± 7.21 vs. 20.44 ± 9.61 days, P<0.001). Furthermore, thrombotic events were strongly associated with adverse clinical outcomes, including a greater requirement for invasive mechanical ventilation (52.9% vs. 29.1%, P=0.001), prolonged ICU length of stay (14.88 ± 7.45 vs. 10.58 ± 5.23 days,

P<0.001), and a higher rate of in-hospital mortality (33.8% vs. 15.9%, P=0.002).

Table 1. Baseline Demographic, Clinical Characteristics, and Vaccination Profiles of the Study Cohort Stratified by Pulmonary Vascular Thrombosis Status

Variable	Total Cohort (N=250)	Thrombosis Group (n=68)	Non-Thrombosis Group (n=182)	Statistical Test	P-value
Age (years), Mean ± SD	58.42 ± 13.65	61.18 ± 12.84	57.39 ± 13.82	t = 1.982	0.049
Male Sex, n (%)	146 (58.4%)	44 (64.7%)	102 (56.0%)	χ^2 = 1.541	0.214
Female Sex, n (%)	104 (41.6%)	24 (35.3%)	80 (44.0%)	χ^2 = 1.541	0.214
Body Mass Index (kg/m²), Mean ± SD	28.74 ± 4.82	30.12 ± 5.16	28.22 ± 4.59	t = 2.809	0.005
Active Tobacco Smoking, n (%)	58 (23.2%)	21 (30.9%)	37 (20.3%)	χ^2 = 3.124	0.077
Arterial Hypertension, n (%)	118 (47.2%)	38 (55.9%)	80 (44.0%)	χ^2 = 2.845	0.092
Type 2 Diabetes Mellitus, n (%)	79 (31.6%)	28 (41.2%)	51 (28.0%)	χ^2 = 3.962	0.047
Coronary Artery Disease, n (%)	48 (19.2%)	17 (25.0%)	31 (17.0%)	χ^2 = 1.942	0.163
Adenoviral Vector Vaccine, n (%)	102 (40.8%)	39 (57.4%)	63 (34.6%)	χ^2 = 10.741	0.001
Inactivated Viral Vaccine, n (%)	148 (59.2%)	29 (42.6%)	119 (65.4%)	χ^2 = 10.741	0.001
Single Vaccine Dose, n (%)	37 (14.8%)	16 (23.5%)	21 (11.5%)	χ^2 = 5.674	0.017
Two Vaccine Doses, n (%)	171 (68.4%)	42 (61.8%)	129 (70.9%)	χ^2 = 1.871	0.171
Booster Dose Received, n (%)	42 (16.8%)	10 (14.7%)	32 (17.6%)	χ^2 = 0.298	0.585
Time from Last Dose to ICU Admission (days), Mean ± SD	18.64 ± 9.45	13.82 ± 7.21	20.44 ± 9.61	t = -5.167	< 0.001
APACHE II Score at Admission, Mean ± SD	16.82 ± 5.34	19.45 ± 5.68	15.84 ± 4.89	t = 4.978	< 0.001
SOFA Score at Admission, Mean ± SD	6.42 ± 2.51	7.85 ± 2.64	5.88 ± 2.26	t = 5.792	< 0.001
Invasive Mechanical Ventilation Requirement, n (%)	89 (35.6%)	36 (52.9%)	53 (29.1%)	χ^2 = 12.023	0.001
ICU Length of Stay (days), Mean ± SD	11.75 ± 6.20	14.88 ± 7.45	10.58 ± 5.23	t = 5.093	< 0.001
In-Hospital Mortality, n (%)	52 (20.8%)	23 (33.8%)	29 (15.9%)	χ^2 = 9.876	0.002

According to the findings presented in Table 2, patients with confirmed pulmonary vascular thrombosis exhibited profound hematologic and coagulopathic alterations, characterized by significantly lower platelet counts (138.26 ± 62.15 vs. 212.71 ± 68.84 ×10⁹/L, P<0.001), a marked prevalence of thrombocytopenia (61.8% vs. 17.6%, P<0.001), and a prominent positivity rate for anti-PF4 antibodies (45.6% vs. 3.8%, P<0.001) relative to non-thrombotic individuals. Furthermore, thrombotic events were accompanied by substantially elevated quantitative D-dimer concentrations (6.84 ± 3.42 vs. 2.22 ± 1.28 mg/L FEU, P<0.001) alongside heightened systemic inflammatory activity, as evidenced by significantly higher serum ferritin (884.60 ± 324.15 vs. 551.76 ± 215.30 ng/mL, P<0.001) and CRP values (104.82 ± 41.55 vs. 68.59 ± 28.74 mg/L, P<0.001). Hemodynamically, patients in the thrombosis cohort displayed severe respiratory and vascular impairment, demonstrated by compromised arterial oxygenation (PaO2/FiO2: 174.60 ± 52.35 vs. 234.84 ± 61.70 mmHg, P<0.001) and significantly elevated pulmonary artery pressures (PASP: 47.85 ± 12.60 vs. 35.20 ± 8.45 mmHg; mPAP: 31.40 ± 8.24 vs. 22.33 ± 4.98 mmHg, both P<0.001).

Table 2. Comparison of Hemodynamic Parameters, Coagulation Profiles, and Inflammatory Biomarkers Stratified by Pulmonary Vascular Thrombosis Occurrence (N=250)

Laboratory and Hemodynamic Parameter	Total Cohort (N=250)	Thrombosis Group (N=68)	Non-Thrombosis Group (N=182)	Statistical Test	P-value
Platelet Count (×10⁹/L), Mean ± SD	192.45 ± 74.32	138.26 ± 62.15	212.71 ± 68.84	t = -7.882	< 0.001
Thrombocytopenia (<150 ×10⁹/L), n (%)	74 (29.6%)	42 (61.8%)	32 (17.6%)	χ^2 = 46.214	< 0.001
Quantitative D-Dimer (mg/L FEU), Mean ± SD	3.48 ± 2.65	6.84 ± 3.42	2.22 ± 1.28	t = 15.684	< 0.001
Plasma Fibrinogen (mg/dL), Mean ± SD	345.80 ± 112.45	278.40 ± 124.60	370.98 ± 96.32	t = -6.175	< 0.001
Prothrombin Time (seconds), Mean ± SD	14.12 ± 2.45	15.68 ± 3.12	13.54 ± 1.84	t = 6.471	< 0.001
International Normalized Ratio (INR), Mean ± SD	1.24 ± 0.28	1.38 ± 0.35	1.19 ± 0.22	t = 5.092	< 0.001
Activated Partial Thromboplastin Time (aPTT, s), Mean ± SD	35.84 ± 6.72	39.42 ± 8.14	34.50 ± 5.58	t = 5.346	< 0.001
Positive Anti-PF4/Polyanion Antibodies, n (%)	38 (15.2%)	31 (45.6%)	7 (3.8%)	χ^2 = 70.825	< 0.001
C-Reactive Protein (CRP, mg/L), Mean ± SD	78.45 ± 36.20	104.82 ± 41.55	68.59 ± 28.74	t = 7.768	< 0.001
Serum Ferritin (ng/mL), Mean ± SD	642.30 ± 285.40	884.60 ± 324.15	551.76 ± 215.30	t = 9.384	< 0.001
Lactate Dehydrogenase (LDH, U/L), Mean ± SD	485.60 ± 178.25	628.40 ± 214.50	432.24 ± 132.80	t = 8.526	< 0.001
PaO2/FiO2 Ratio (mmHg), Mean ± SD	218.45 ± 64.80	174.60 ± 52.35	234.84 ± 61.70	t = -7.218	< 0.001
Peripheral Oxygen Saturation (SpO2, %), Mean ± SD	89.65 ± 5.12	86.80 ± 5.64	90.72 ± 4.45	t = -5.751	< 0.001
Pulmonary Artery Systolic Pressure (PASP, mmHg), Mean ± SD	38.64 ± 11.25	47.85 ± 12.60	35.20 ± 8.45	t = 8.942	< 0.001
Mean Pulmonary Artery Pressure (mPAP, mmHg), Mean ± SD	24.80 ± 7.15	31.40 ± 8.24	22.33 ± 4.98	t = 10.428	< 0.001

As shown in Table 3, adenoviral vector vaccination, a shorter interval between the last vaccine dose and ICU admission, higher baseline SOFA scores, elevated D-dimer concentrations, thrombocytopenia, anti-PF4 antibody positivity, impaired oxygenation, and increased PASP remained independently associated with pulmonary vascular thrombosis in the multivariable model. The strongest associations were observed for anti-PF4 antibody positivity (adjusted OR:6.842; 95% CI:2.418-19.362; P<0.001), thrombocytopenia (adjusted OR:3.428; 95% CI:1.584-7.418; P=0.002), and adenoviral vector vaccination (adjusted OR, 2.815; 95% CI:1.382-5.735; P=0.004). D-dimer elevation, shorter post-vaccination intervals, higher SOFA scores, lower PaO_2/FiO_2 ratios, and increased PASP also demonstrated statistically significant associations, whereas age, sex, body mass index, diabetes, and ferritin were not independent predictors after adjustment.

Table 3. Univariate and Multivariate Logistic Regression Analyses Identifying Independent Predictors of Acute Pulmonary Vascular Thrombosis in ICU Patients (N=250)

Predictor Variable	Univariate Analysis: Crude OR (95% CI)	Univariate P-value	Multivariate Analysis: Adjusted OR (95% CI)	Multivariate P-value
Age (per 1-year increase)	1.021 (0.999 - 1.044)	0.052	1.012 (0.985 - 1.040)	0.385
Male Sex (vs. Female)	1.442 (0.810 - 2.568)	0.216	1.218 (0.612 - 2.424)	0.574
Body Mass Index (per 1 kg/m² increase)	1.088 (1.025 - 1.155)	0.006	1.054 (0.981 - 1.132)	0.152
Type 2 Diabetes Mellitus (Presence vs. Absence)	1.800 (1.008 - 3.214)	0.047	1.342 (0.672 - 2.680)	0.404

Adenoviral Vector Vaccine (vs. Inactivated Platform)	2.544 (1.442 - 4.489)	0.001	2.815 (1.382 - 5.735)	0.004
Time from Last Dose to ICU Admission (per day decrease)	1.084 (1.046 - 1.124)	< 0.001	1.062 (1.018 - 1.108)	0.006
Baseline SOFA Score (per 1-point increase)	1.385 (1.218 - 1.575)	< 0.001	1.204 (1.025 - 1.414)	0.024
Quantitative D-Dimer (per 1 mg/L FEU increase)	2.458 (1.954 - 3.092)	< 0.001	1.982 (1.512 - 2.598)	< 0.001
Thrombocytopenia (<150 ×10⁹/L vs. Normal Count)	7.587 (4.045 - 14.230)	< 0.001	3.428 (1.584 - 7.418)	0.002
Positive Anti-PF4 Antibodies (vs. Negative Status)	20.957 (8.628 - 50.903)	< 0.001	6.842 (2.418 - 19.362)	< 0.001
Serum Ferritin (per 100 ng/mL increase)	1.482 (1.325 - 1.658)	< 0.001	1.145 (0.988 - 1.327)	0.071
PaO2/FiO2 Ratio (per 10 mmHg decrease)	1.182 (1.118 - 1.250)	< 0.001	1.094 (1.015 - 1.179)	0.019
PASP (per 5 mmHg increase)	1.624 (1.412 - 1.868)	< 0.001	1.286 (1.068 - 1.548)	0.008

Discussion

The present investigation provides a comprehensive evaluation of the incidence, clinical correlates, and independent predictors of acute pulmonary vascular thrombosis among critically ill patients admitted to intensive care units following COVID-19 vaccination. In our cohort of 250 individuals, the incidence of radiologically verified pulmonary vascular thrombosis was 27.2%, characterizing an acute, life-threatening vascular complication within critical care settings. Patients developing pulmonary thrombosis exhibited markedly elevated physiological acuity upon admission, demonstrated by significantly higher APACHE II and SOFA scores, a heightened requirement for invasive mechanical ventilation, and increased in-hospital mortality compared to non-thrombotic counterparts. Biochemically and immunologically, the thrombosis cohort displayed severe consumptive coagulopathy and systemic hyperinflammation, characterized by marked thrombocytopenia, steep D-dimer elevations, hypofibrinogenemia, elevated ferritin and CRP levels, and a substantial seropositivity rate for anti-platelet factor 4 (anti-PF4) antibodies. Multivariable logistic regression identified anti-PF4 antibody seropositivity, baseline thrombocytopenia, administration of adenoviral vector-based vaccines, elevated D-dimer concentrations, admission SOFA score, elevated pulmonary artery pressures, and a shorter latency between vaccination and ICU admission as robust independent predictors of pulmonary vascular thrombosis [6,7].

The biological association between adenoviral vector-based vaccination and the profound escalation in pulmonary vascular thrombotic events observed in this cohort reflects the pathological cascade of vaccine-induced immune thrombotic thrombocytopenia (VITT). Unlike inactivated viral platforms, replication-deficient adenoviral vectors can trigger strong cross-reactivity and innate immune activation through electrostatic interactions with circulating polyanions and endogenous human platelet factor 4. Positively charged PF4 tetramers undergo conformational modification upon binding negatively charged vector components or residual manufacturing chaperones, displaying immunogenic neoepitopes. This macromolecular clustering prompts B-cell clones to synthesize high-titer IgG antibodies directed against PF4 polyanion complexes. When these anti-PF4 antibodies bind platelet surfaces, their crystallizable fragment (Fc) domains cross-link the low-affinity platelet FcγRIIa receptors, initiating unrestrained, autonomous platelet activation, degranulation, and rapid intravascular aggregation that manifest clinically as microvascular and macrovascular thrombosis [8, 9]. The significant systemic consumption and clearance of activated thrombocytes explain the intense thrombocytopenia seen in over sixty percent of our thrombotic cohort. Circulating immune complexes of anti-PF4 autoantibodies and PF4 tetramers activate platelets and trigger their immediate sequestration and clearance by tissue macrophages within the reticuloendothelial system of the spleen and liver. Concurrently, activated platelets shed dense and alpha granules, expelling abundant prothrombotic mediators, including thromboxane A2, adenosine diphosphate, and additional free PF4, which creates an autocrine and paracrine feed-forward loop of continuous cell recruitment. Extensive intravascular platelet-rich microthrombi exhaust the circulating pool faster than megakaryocyte thrombopoiesis can replenish it. The strong adjusted odds ratio demonstrating thrombocytopenia as an independent predictor emphasizes that a drop in peripheral platelet count following adenoviral vaccination is a hallmark of

consumptive immunothrombosis rather than benign bone marrow suppression [10,11].

Intravascular platelet cross-linking initiates robust functional recruitment of monocytes and neutrophils, establishing a crucial bridge between sterile post-vaccination inflammation and widespread pulmonary thrombosis. Stimulated monocytes markedly upregulate surface tissue factor expression, igniting the extrinsic coagulation pathway and transforming prothrombin into active thrombin. Concomitantly, activated neutrophils undergo programmed extrusion of decondensed chromatin, citrullinated histones, and primary granule proteases into the circulation, forming dense networks known as neutrophil extracellular traps (NETs). These NETs supply a negatively charged scaffold that stabilizes fibrin strands, entraps red blood cells, and activates coagulation factor XII, accelerating contact-dependent intrinsic thrombin propagation. This reciprocal amplification between ongoing immunogenic platelet activation and leukocyte-mediated thrombin generation explains why patients developing pulmonary thrombosis displayed markedly higher circulating CRP, LDH, and ferritin values alongside overt laboratory signs of consumptive coagulopathy [12,13].

The dramatic surge in quantitative D-dimer concentrations and prolonged clotting parameters reflect explosive, widespread fibrin generation coupled with secondary endogenous fibrinolysis within the pulmonary vasculature. Thrombin burst on the negatively charged procoagulant membrane of ballooned platelets converts soluble circulating fibrinogen into cross-linked insoluble fibrin polymers, explaining the lower baseline fibrinogen levels observed in our thrombotic group. Endogenous tissue plasminogen activator released from damaged vascular beds cleaves this dense meshwork, releasing massive amounts of cross-linked fibrin degradation products that elevate D-dimer titers. Elevated D-dimer served as a consistent independent marker of acute clot burden in our regression model, proving that intense fibrin turnover is active even when peripheral vascular thrombosis remains occult or localized to subsegmental pulmonary arteries [14,15].

Hemodynamically, pulmonary vascular thrombosis was accompanied by severe impairments in oxygenation and profound pulmonary arterial hypertension, evidenced by diminished PaO2/FiO2 ratios and elevated PASP and mPAP values. Intravascular thrombi obstructing the pre-capillary pulmonary arterial branches produce physical mechanical occlusion, creating expansive alveolar dead-space compartments where ventilated alveolar units receive zero capillary perfusion. Simultaneously, active secretion of potent vasoactive mediators from aggregating platelets particularly serotonin, thromboxane A2, and endothelin-1 induces acute, intense precapillary vasoconstriction across intact vascular beds, shunting deoxygenated blood through non-ventilated lung territories and generating severe intrapulmonary ventilation-perfusion mismatch and refractory hypoxemia. This sudden, massive increase in pulmonary vascular resistance imposes acute afterload strain on the thin-walled right ventricle, provoking progressive chamber dilation, tricuspid regurgitation, and functional right-sided systolic failure [16,17].

The substantial latency gradient observed between last vaccine exposure and critical care presentation where thrombotic patients presented significantly sooner after vaccination than non-thrombotic controls sheds light on the kinetics of vaccine-induced autoantibody generation. Secondary humoral immune pathways typically require approximately five to twenty days to mount sufficient IgG anti-PF4 titers to overcome endogenous immunoregulatory thresholds and provoke systemic platelet clustering. Patients admitted earlier within this window exhibited rapid, fulminant immune stimulation characterized by high antibody affinities and rapid antibody-mediated cell activation. In contrast, non-thrombotic critical illness admissions presenting at later post-vaccine timepoints were largely driven by intercurrent secondary bacterial superinfections, underlying cardiovascular decompensation, or exacerbations of chronic pulmonary disorders rather than acute, antibody-mediated thrombotic complications [18,19].

The marked prognostic impact of thrombosis on invasive ventilation, ICU length of stay, and in-hospital mortality underscores the catastrophic convergence of systemic organ dysfunction and acute vascular insult in these patients. In individuals with preexisting baseline disease and critical organ stress, as evidenced by elevated baseline SOFA and APACHE II scores, the sudden superimposition of microvascular thrombosis compromises coronary, renal, and cerebral microcirculations alongside pulmonary compromise. Severe micro thrombotic occlusion and local cytokine release disrupt endothelial barrier stability, promoting capillary leak, alveolar flooding, and rapid progression toward acute respiratory distress syndrome that mandates immediate endotracheal intubation. The resulting hemodynamic instability, compounded by elevated intrathoracic pressures during positive-pressure ventilation, worsens right ventricular forward failure, culminating in cardiogenic shock, persistent multi-organ hypoperfusion, prolonged ICU dependency, and premature mortality [20,21].

Our findings have direct implications for intensive care triaging, protocolized risk stratification, and targeted pharmacotherapeutic management of critically ill post-vaccine presentations. Given the high predictive value of anti-PF4 antibody seropositivity, profound thrombocytopenia, and

sharp D-dimer spikes, clinicians must implement low-threshold screening protocols that bundle standard hemograms with rapid enzyme immunoassays for anti-PF4 antibodies in patients presenting with unexplained acute respiratory failure or hemodynamic collapse following vaccination. Confirming an immune-mediated thrombotic process necessitates immediate avoidance of unfractionated or low-molecular-weight heparins, which can perpetuate or aggravate PF4 complexation and exacerbate catastrophic platelet aggregation. Instead, therapeutic regimens should promptly shift toward non-heparin direct thrombin inhibitors or factor Xa antagonists, complemented by high-dose intravenous immunoglobulins to saturate and neutralize platelet FcγRIIa receptors, downregulating the devastating autoimmune prothrombotic drive [22,23].

Conclusion

Post-vaccination pulmonary vascular thrombosis in critically ill patients is independently driven by adenoviral vector platforms, thrombocytopenia, and anti-PF4 seropositivity, leading to marked hemodynamic compromise. Routine screening with D-dimer, platelet counts, and anti-PF4 antibody assays facilitates early risk stratification, timely intervention, and mitigated ICU mortality.

Disclosure Statement

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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