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Perspective

Platelet count as an important prognostic factor for vaccine-induced immune thrombotic thrombocytopenia

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Introduction

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported in a patient after receiving two vaccines with a recombinant adenoviral vector encoding the spike glycoprotein of coronavirus disease (COVID-19) in Europe and the United States [1, 2]. Among approximately 12.7 million people who received ChAdOx1 nCov-19 (AstraZeneca) vaccines in Korea [3], we detected two cases of cerebral venous sinus thrombosis together with thrombocytopenia and positive results for platelet factor 4 (PF4)–heparin antibody using enzyme-linked immunosorbent assay (ELISA). The fatality rate in our study was 50%. This study aimed to analyze a suitable prognostic factor through a central review of domestic cases and a literature review of overseas reports.

Clinical and laboratory characteristics of 44 VITT patients

We reviewed two Korean patients and previously reported 42 patients [1, 4-6] with VITT onset after receiving AstraZeneca vaccines in this study. We excluded one reported case from England because PF4-heparin antibody was not detected using two ELISA methods [5]. In total, 44 patients were selected for inclusion in this analysis (Table 1), composed of 17 and 27 male and female patients, respectively, showing a female predominance, and with a median age of 36 years (range, 21–77 yr). Initial symptoms appeared at a median of 10 days after vaccination (range, 5–24 days). Symptoms were analyzed in only 10 patients; headache was the most common symptom related to cerebral venous thrombosis (CVT). CVT was detected in 29 patients, including the 2 Korean cases, which was the most frequent site in 66% of the total patients. Six patients showed combined cerebral hemorrhage among 29 CVT cases. Pulmonary embolism was diagnosed in 12 (27%) patients, and arterial and splanchnic vein thromboses were detected in 10 (23%) and 8 (18%) patients, respectively.

All cases showed decreased platelet counts and elevated D-dimer levels, both at initial presentation [5, 6] and during treatment [1, 4, 6]. The initial and nadir platelet counts were available for 26 and 21 cases, respectively. The median platelet counts (range) initially and at nadir were 35,000 (7,000–113,000) and 23,000 (8,000–107,000) (reference range, 150,000–440,000/μL). All except two cases had positive results for PF4–heparin antibody on ELISA, but

Table 1. Clinical and laboratory characteristics of patients with vaccine-induced immune thrombotic thrombocytopenia (VITT).

Patient No.	Age, years	Sex	Symptom onset (N of days after vaccination)	Symptoms	CVT	Splanchnic vein thrombosis[a]	Pulmonary embolism	Other thrombosis or hemorrhage	Platelet initial (per μL)	Platelet nadir (per μL)	D-dimer, peak (mg/L)	INR peak	PTT peak (sec)	Fibrinogen nadir (mg/dL)	PF4–heparin ELISA (optical density)	Heparin treatment	Other medical conditions	Outcome
Korean 1	33	M	11	Headache, seizure	Yes	No	No	Cerebral hemorrhage	77,000	65,000	>20	1.01	35.7	197.9	3.10	No	ACL-Ab	Full recovery
Korean 2	33	M	8	Headache, hemiparesis, drowsiness	Yes	No	No	Cerebral hemorrhage	14,000	10,000	>35.2	1.51	60.7	77	0.72	No	No	Fatal
Ref 1-1	NA	NA	5	Chills, fever, nausea, and epigastric discomfort	Yes	Yes	Yes	Aortoiliac artery thrombosis	NA	13,000	142	1.4	41.6	78	3.16	Yes	No	Fatal
Ref 1-2	NA	NA	6	NA	No	No	Yes	No	NA	107,000	1.8	1.12	29	568	3.08	LMWH[e]	No	Recovering
Ref 1-3	NA	NA	9	NA	Yes	No	No	No	NA	60,000	13	NA	NA	NA	3.5	Unknown	No	Unknown
Ref 1-4	NA	NA	7	NA	Yes	No	No	No	NA	9,000	NA	1.66	46.6	NA	3.4	Yes	CND	Fatal
Ref 1-5	NA	NA	13	NA	Yes	Yes	Yes	Right intra-ventricular, iliofemoral vein, IVC thrombi	NA	23,000	NA	1.25	64.8	173	1.2	Yes	VWD-I; FVL; ACL-Abs	Recovering
Ref 1-6	NA	NA	7	NA	Yes	No	No	No	NA	75,000	2.6	1.05	23	NA	NA	Unknown	No	Recovering
Ref 1-7	NA	NA	8	NA	Yes	No	No	No	NA	29,000	>33.0	1.34	45	210	NA	Yes	No	Recovering
Ref 1-8	NA	NA	8	NA	Yes	No	No	Widespread microvascular thrombi (brain, lungs, and kidneys)[d]	NA	16,000	NA	NA	NA	NA	2.02	No	No	Fatal
Ref 1-9	NA	NA	16	NA	Yes	No	No	Multiple organ thrombi[d]	NA	13,000	21	1.7	46.1	40	3.51	No	No	Fatal
Ref 1-10	NA	NA	11	NA	Yes	Yes	No	No	NA	8,000	>35.0	NA	NA	80	2.35	No	No	Fatal
Ref 1-11	NA	NA	12[b]	NA	Pending[c]	No	No	Cerebral hemorrhage[c]	NA	NA	NA	NA	NA	NA	2.16	No	Unknown	Fatal
Ref 4-1	37	F	8	Fever, headache, visual disturbances	Yes	No	No	No	NA	22,000	>35	1.2	25	210	3.7	Initial low dose of LMWH	NA	Fatal
Ref 4-2	42	F	10	Headache, drowsiness	Yes	No	No	No	NA	14,000	>35	1	31	80	35.93.4	Reduced dose of LMWH	NA	Fatal
Ref 4-3	32	M	7	Back pain	No	Yes	No	Azygos vein, hemiazygos vein, and several basivertebral veins' thrombi	NA	10,000	>35	1.1	25	230	3.6	Reduced dose of LMWH	NA	Full recovery
Ref 4-4	39	F	10	Headache, abdominal pain	Yes	No	No	No	NA	70,000	13	1.3	25	120	3.8	Reduced dose of LMWH	NA	Full recovery
Ref 4-5	54	F	7	Headache, hemiparesis	Yes	No	No	No	NA	19,000	>35	1.1	29	120	2.9	Heparin (5,000 IU)	NA	Fatal
Ref 5-1	30	F	13	NA	Yes	Yes	Yes	Ischemic bowel with infarction	27,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-2	55	F	6	NA	No	Yes	No	Acute aortic thrombosis and cerebral hemorrhage	11,000	NA	NA	NA	NA	NA	Pos	NA	NA	Died
Ref 5-3	26	F	12	NA	Yes	No	No	No	64,000	NA	NA	NA	NA	NA	2.45	NA	NA	Survived
Ref 5-4	52	F	10	NA	Yes[d]	No	Yes[d]	Cerebral hemorrhage[d]	31,000	NA	NA	NA	NA	NA	2.26	NA	NA	Died
Ref 5-5	38	M	14	NA	No	No	Yes	No	16,000	NA	NA	NA	NA	NA	2.84	NA	NA	Died
Ref 5-6	49	F	15	NA	Yes	No	Yes	Cerebral hemorrhage	14,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-7	25	M	9	NA	Yes	No	No	No	19,000	NA	NA	NA	NA	NA	Pos	NA	NA	Died
Ref 5-8	32	M	19	NA	Yes	No	No	No	87,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-9	35	F	9	NA	Yes	No	No	No	65,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-10	77	M	8	NA	No	No	Yes	No	NA	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-11	66	M	12	NA	No	No	No	Deep vein thrombosis, adrenal hemorrhage	34,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-12	34	M	14	NA	Yes	No	No	No	23,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-13	54	M	10	NA	No	Yes	No	Myocardial infarction	71,000	NA	NA	NA	NA	NA	0.76	NA	NA	Died

Table 1. Continued.

Patient No.	Age, years	Sex	Symptom onset (N of days after vaccination)	Symptoms	CVT	Splanchnic vein thrombosis[a]	Pulmonary embolism	Other thrombosis or hemorrhage	Platelet initial (per μL)	Platelet nadir (per μL)	D-dimer, peak (mg/L)	INR peak	PTT peak (sec)	Fibrinogen nadir (mg/dL)	PF4–heparin ELISA (optical density)	Heparin treatment	Other medical conditions	Outcome
Ref 5-14	71	F	14	NA	No	No	No	Hemorrhagic symptoms only	17,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-15	22	F	10	NA	Yes	No	No	Cerebral hemorrhage	100,000	NA	NA	NA	NA	NA	1.4	NA	NA	Died
Ref 5-16	39	F	10	NA	No	No	No	Cerebral infarction	57,000	NA	NA	NA	NA	NA	1.4	NA	NA	Survived
Ref 5-17	70	F	17	NA	No	No	Yes	Deep vein thrombosis	28,000	NA	NA	NA	NA	NA	Pos	NA	NA	Survived
Ref 5-18	21	M	10	NA	No	No	No	Cerebral infarction	113,000	NA	NA	NA	NA	NA	2.8	NA	NA	Survived
Ref 5-19	46	F	14	NA	Yes	No	No	No	7,000	NA	NA	NA	NA	NA	>3.00	NA	NA	Survived
Ref 5-20	32	F	12	NA	Yes	No	No	No	98,000	NA	NA	NA	NA	NA	2.17	NA	NA	Died
Ref 5-21	48	M	14	NA	Yes	No	No	No	16,000	NA	NA	NA	NA	NA	2.45	NA	NA	Survived
Ref 5-22	49	F	24	NA	No	No	Yes	No	61,000	NA	NA	NA	NA	NA	>3.00	NA	NA	Survived
Ref 6-1	72	F	7	Leg pain, claudication	No	No	No	Peripheral artery thromboses	36,000	39,000	>20	NA	NA	237	2.70	Yes	NA	Full recovery
Ref 6-2	63	M	18	Leg clamping	No	No	Yes	Peripheral artery thromboses, deep vein thrombosis	36,000	26,000	>10	1.3	NA	140	1.78	Yes	NA	Full recovery
Ref 6-3	69	M	12	Headache, confusion	Yes	Yes	Yes	Cerebral infarction, internal jugular vein thrombosis	35,000	29,000	3.35	1.4	NA	210	2.69	No	NA	Recovering

[a]Splanchnic-vein thrombosis indicates thrombosis of the portal, mesenteric, splenic, or hepatic veins.
[b]The day when the body of the deceased was found.
[c]Brain neuropathological results were pending at time of this report; CVT had not been ruled out.
[d]These were the postmortem findings.
[e]Treatment with low-molecular-weight heparin was associated with clinical improvement and increasing platelet counts (107,000 to 132,000 over 3 days). The patient's drug was then switched to a direct oral anticoagulant when the ELISA showed positive results for antibodies against PF4–heparin, with further clinical and platelet-count recovery.
Abbreviations: ACL-Abs, anticardiolipinantibodies; CVT, cerebral venous (sinus) thrombosis of the cortical vein; ELISA, enzyme-linked immunosorbent assay; F, female; FVL, factor V Leiden; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; M, male; NA, not available; PF4, platelet factor 4; Pos, positive; PTT, partial thromboplastin time; VWD-I, type 1 von Willebrand disease.

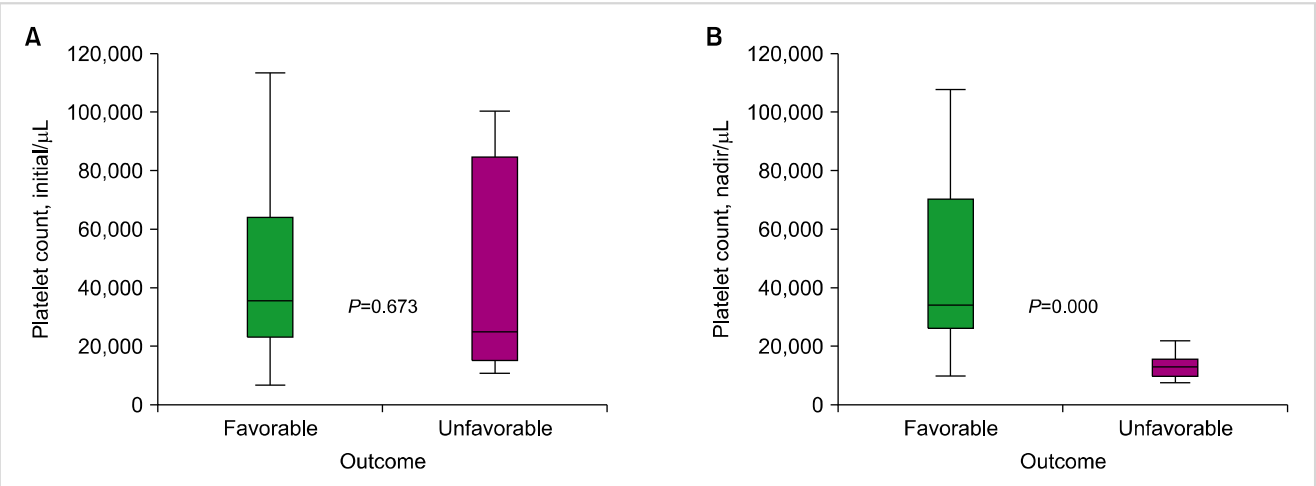

Fig. 1. Comparison of the distribution of the initial **(A)** and nadir **(B)** platelet counts between patients with favorable outcomes and those with unfavorable outcomes.

the quantitative value did not correlate with the clinical outcome. Data on peak prothrombin time, activated partial thromboplastin time, and fibrinogen level at nadir were available in our report and two other reports [1, 4], revealing disseminated intravascular coagulation features in some patients. However, this finding was not associated with mortality.

Platelet counts according to clinical outcomes in VITT

When comparing patients with favorable outcomes (recovery or full recovery) and those with unfavorable outcomes (fatal/died), the initial platelet counts between the groups were not significantly different in 26 patients, as determined using the nonparametric test (median, 35,500 and 23,000/μL). In contrast, the nadir platelet counts during the clinical course in 10 patients with favorable outcomes were significantly higher than those of 9 patients with unfavorable outcomes (median, 34,000 and 13,000/μL) (Fig. 1). The cutoff value for predicting fatality based on the nadir platelet count was 22,000/μL, as determined using a receiver operating characteristic curve, with an area under the curve of 0.928 (Fig. 2).

Discussion

In Korea, adenovirus-based COVID-19 vaccines were banned for those in their 20s and permitted only for those ≥30-years-old since April 25, 2021, after performing the risk-benefit assessment when comparing severe hospitalization and mortality rates after COVID-19 with the predicted mortality of VITT [7]. Moreover, an active surveillance system involving a self-monitoring application that enabled early declaration and inspection was maintained for people receiving AstraZeneca and Janssen vaccines. Tests for the PF4-heparin antibody were performed in a central laboratory. Among the 35 suspected thrombocytopenia and/or thrombosis cases, two were confirmed as VITT [8]. The relatively low incidence of two VITT cases among 12.7 million individuals when compared with that in Western countries (348 cases among 14.3 million individuals receiving AstraZeneca vaccination in the UK, 32 cases among 10.2 million individuals receiving Janssen vaccination in the USA) [9, 10] should be considered when preparing the vaccination guidelines for each country.

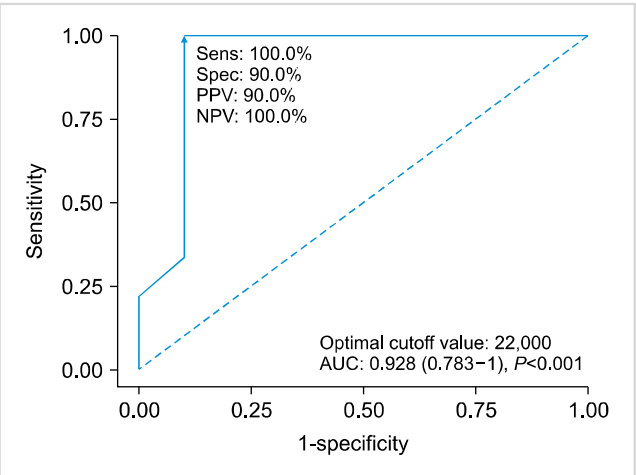

Fig. 2. Receiver operating characteristic curve to predict the prognosis of vaccine-induced immune thrombotic thrombocytopenia (VITT) with the nadir platelet count.

Rapid deterioration and fatality due to VITT were the main problems during the early periods, until we elucidated the exact mechanism of the disease. The key pathophysiology causing both thrombosis and bleeding is based on an autoantibody-mediated immune response, similar to heparin-induced thrombocytopenia. Therefore, the induction of immune tolerance through the administration of immunoglobulin and steroids is recommended as an effective treatment. The administration of anticoagulants other than heparin and low-molecular-weight heparin should be considered to improve the clinical course of thrombosis [11]. However, this study revealed that patients with severe thrombocytopenia at presentation or patients who failed to recover their platelet counts during treatment with immunosuppressants and those who bypassed anticoagulants may have a poor prognosis. This is the first important and significant recommendation globally, although only a few VITT cases have been reported, and their numbers are smaller than those reported in each country's media. Our study findings suggest the following recommendations: 1) Individuals who receive AstraZeneca and Janssen vaccines should be educated about visiting the hospital immediately if they experience symptoms possibly related to thrombosis and thrombocytopenia between 4 days and 4 weeks after vaccination (suspected cases). 2) Medical staff in hospitals, including primary clinics, should immediately request PF4/heparin antibody tests to the central laboratory if they screened cases of thrombocytopenia and thrombosis through blood and imaging tests (presumed cases). 3) Patients with thrombocytopenia and thrombosis with positive results for PF4/heparin antibody should be treated with immunoglobulins, steroids, and substitutive anticoagulants (confirmed cases). In conclusion, we cautiously suggest that early diagnosis of VITT after symptom development is the most important aspect in reducing VITT-related fatality. Furthermore, clinicians should consider more active measures, such as plasma exchange, early when they detect patients whose initial or subsequent platelet counts are less than 22,000/μL.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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