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Thrombosis patterns and clinical outcome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To meta-analyse the clinical manifestations, diagnosis, treatment, and mortality of vaccine-induced immune thrombotic thrombocytopenia (VITT) after adenoviral vector vaccination.
Methods: Eighteen studies of VITT after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccine administration were reviewed from PubMed, Scopus, Embase, and Web of Science. The meta-analysis estimated the summary effects and between-study heterogeneity regarding the incidence, manifestations, sites of thrombosis, diagnostic findings, and clinical outcomes.
Results: The incidence of total venous thrombosis after ChAdOx1 nCoV-19 vaccination was 28 (95% CI 12-52, I^2=100%) per 100,000 doses administered. Of 664 patients included in the quantitative analysis (10 studies), the mean age of patients with VITT was 45.6 years (95% CI 43.8-47.4, I^2=57%), with a female predominance (70%). Cerebral venous thrombosis (CVT), deep vein thrombosis (DVT)/pulmonary thromboembolism (PE), and splanchnic vein thrombosis occurred in 54%, 36%, and 19% of patients with VITT, respectively. The pooled incidence rate of CVT after ChAdOx1 nCoV-19 vaccination (23 per 100,000 person-years) was higher than that reported in the pre-pandemic general population (0.9 per 100,000 person-years). Intracranial haemorrhage and extracranial thrombosis accompanied 47% and 33% of all patients with CVT, respectively. The antiplatelet factor 4 antibody positivity rate was 91% (95% CI 88-94, I^2=0%) and the overall mortality was 32% (95% CI 24-41, I^2=69%), and no significant difference was observed between heparin- and non-heparin-based anticoagulation treatments (risk ratio 0.84, 95% CI 0.47-1.50, I^2=0%).
Conclusions: Patients with VITT after SARS-CoV-2 vaccination most frequently presented with CVT following DVT/PE and splanchnic vein thrombosis, and about one-third of patients had a fatal outcome. This meta-analysis should provide a better understanding of VITT and assist clinicians in identifying VITT early to improve outcomes and optimise management.

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Introduction

More than 233 million people have been infected with SARS-CoV-2, and 4.7 million people have died of the disease worldwide (as of 1 October 2021). Several vaccines have been developed concerning this public health problem, and 6.2 billion doses have already been administered (COVID-19 Map - Johns Hopkins Coronavirus Resource Center, October 1, 2021). A phase-III clinical trial of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine included 12,021 participants from the United Kingdom, Brazil, and South Africa, and reported no adverse events related to unusual thrombotic events (Voysey et al., 2021). However, as the ChAdOx1 nCoV-19 vaccination programmes expanded, reports of rare events of thrombosis began emerging from March 2021 (Greinacher et al., 2021a; Schultz et al., 2021; Scully et al., 2021). Because of safety concerns related to thrombosis, several European countries re-evaluated the eligibility criteria, with many of them recommending against ChAdOx1 nCoV-19 vaccine administration in people under the age of 50. After receiving more reports from various countries, clinicians named this rare adverse event vaccine-induced immune thrombotic thrombocytopenia (VITT), reflective of its similarity in pathophysiology to heparin-induced thrombocytopenia (HIT). A similar adverse event was observed in another adenovirus vector vaccine (Ad26.COV2.S; Johnson & Johnson) (See et al., 2021).

Subsequently, the first case series of VITT was published in April 2021 (Greinacher et al., 2021), and it suggested the benefit of the antiplatelet factor 4 (anti-PF4) antibody test for diagnosing VITT. Later, Hwang et al. summarised case reports related to VITT and introduced several prognostic factors related to mortality (Hwang et al., 2021). However, because of the different clinical environments among studies, comprehensively describing VITT has been challenging.

Thus, we conducted a systematic review and meta-analysis to assess patient demographics, clinical manifestations, laboratory findings, patterns of treatment, and mortality for VITT after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination. We expect our meta-analysis to provide clinicians with a thorough understanding of this rare adverse event.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for this systematic review (Supplementary Table S1), and this study was not registered with the International Prospective Register of Systematic Reviews (PROSPERO) because of concerns regarding sensitive information related to an evolving and topical area of research.

Literature Search Strategy and Study Selection

Two investigators (A.Y.K. and W.W.) searched PubMed, Scopus, Embase, and Web of Science databases up to 4 October 2021 to identify studies that reported VITT after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination. Our initial search yielded 725 articles. After a review of individual abstracts and full texts, we identified 18 studies (Abbattista et al., 2021; Gras-Champel et al., 2021; Greinacher et al., 2021b; Hippisley-Cox et al., 2021; Huh et al., 2021; Krzywicka et al., 2021; Pavord et al., 2021; Perry et al., 2021; Pottegård et al., 2021; Rosenblum et al., 2021; Sánchez van Kammen et al., 2021a; Schultz et al., 2021; Schulz et al., 2021; Scully et al., 2021; See et al., 2021; de Simone et al., 2021; Simpson et al., 2021; Tiede et al., 2021) (4 case series, 7 cohort studies, 1 monthly report, 1 brief communication, 2 narrative reviews, 1 observational study, and 2 self-controlled case series) that met our inclusion criteria. The search terms used are described in Supplementary Table S2. Discrepancies regarding the inclusion/exclusion of studies were discussed and resolved by consensus among 3 investigators (J.I.S., A.Y.K, and W.W.). The full literature search strategy is presented in Supplementary Figure S1. The eligibility criteria included studies in which: (1) venous thrombosis, thrombotic thrombocytopenia, or VITT were an adverse event following ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination; (2) cerebral venous thrombosis (CVT) developed after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination; and (3) an editorial, short survey, or monthly report to identify the most recent comprehensive analysis of incidence was manually added. We excluded: (1) studies in which VITT was reported before the COVID-19 pandemic; (2) case series with less than 5 cases; (3) review articles, letters to the editors, abstracts, and articles with insufficient patient information; and (4) studies with insufficient patient data. We finally included 18 studies that met the inclusion criteria. Among them, 10 studies with clinical data were subsequently used to analyse clinical manifestations and outcomes. The remaining 8 were used to analyse the incidence of VITT. The summary of the included studies' findings is shown in Supplementary Table S3.

Definition of VITT

The inclusion criteria for VITT of each study are described in Supplementary Table S4. All studies suggested several criteria, such as recent vaccination history, presence of thrombosis, thrombocytopenia, D-dimer levels, results of anti-PF4 antibody tests, and additional experts' opinion.

Data Extraction

For each eligible clinical trial (or study), we recorded the first author, publication year, journal name, country, total number of patients, incidence proportion or incidence rate of patients who developed any type of thrombosis, patients' demographics, location of thrombosis, laboratory results, treatment modalities, clinical course, and patient survival.

Analyses of Clinical Studies and Statistical Analysis

The data for each study that was included in the clinical analysis are presented in Table 1 (Greinacher et al., 2021b; Krzywicka et al., 2021; Pavord et al., 2021; Perry et al., 2021; Sánchez van Kammen et al., 2021a; Schultz et al., 2021; Schulz et al., 2021; Scully et al., 2021; See et al., 2021; Tiede et al., 2021). To estimate the proportion of patients with VITT for each variable, we performed a meta-analysis to estimate the summary effects with a proportion of each variable and 95% confidence interval (CI) using random-effects models (DerSimonian and Laird, 2015; Lau et al., 1997). The random-effects model provides the weighted average of the effect sizes of a group of studies with the assumption that each study supplies information about a different effect size (Ioannidis et al., 2011). We evaluated the between-study heterogeneity using the I^2 metric of inconsistency and P-value of the Cochran Q test. I^2 is the ratio of the between-study variance to the sum of the within-study and between-study variances, ranging from 0–100%. I^2 values over 50% usually represent significant heterogeneity (Higgins et al., 2003).

Publication bias was not assessed because studies included in the proportion meta-analyses were non-comparable except for the mortality comparison between 2 types of anticoagulation. All analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The pooled incidence of VITT (total venous or CVT) after SARS-CoV-2 vaccinations (ChAdOx1 nCoV-19, Ad26.COV2.S) is shown in

Table 1
Characteristics and laboratory findings of patients with vaccine-induced immune thrombotic thrombocytopenia (VITT) after ChAdOx1 nCov-19 or Ad26.COV2.S vaccination

Author, year	Country	N participants	Age, Median (IQR or range)	Female (%)	Location of thrombosis					Laboratory findings[a]					
					CVT	CVT with PE	ICH	SVT	PE	Platelet cells × 10^9/L	PT (sec) or INR	aPTT, sec	Fibrinogen g/L	D-dimer	Positive Anti-PF4 Ab (%)
Perry, 2021 (Perry et al., 2021)	UK	70	47 (32-55)	31/70 (44.3)	70/70 (100.0)	14/70 (20.0)	-	-	-		13.0 (11.9-14.8)	28.8 (25.1-34.8)	2.0 (1.3-2.8)	-	56/58 (96.6)
Tiede, 2021 (Tiede et al., 2021)	Germany	5	61 (61-63)	5/5 (100.0)	1/5 (20.0)		1/5 (20.0)	1/5 (20.0)	-	40 (27-62)	-	-	-	5/5 (100) over 22.4mg/L	-
Krzywicka, 2021 (Krzywicka et al., 2021)	Eudravigillance	187	46 (32-56)	138/184 (75.0)	187/187 (100.0)	9/187 (4.8)	-	-	-	31[f] (17-64)	-	-	-	-	15[f]
Schulz, 2021 (Schulz et al., 2021)	Germany	53	-	-	37/53 (69.8)	-	-	-	-	-	-	-	-	-	-
See, 2021 (See et al., 2021)	USA	12	18-60[b]	12/12 (100.0)	12/12 (100.0)	3/12 (25.0)	7/12[d] (58.3)	-	-	19[e] (12.8-74.3)	INR 1.2 (1.1-1.25)	28 (25.3-31)	1.45[¶] (0.90-2.14)	8.15mg/L[e] (6.8-34.7)	11/11 (100.0)
Scully, 2021 (Scully et al., 2021)	UK	23	46 (21-77)[b]	14/23 (60.9)	13/23 (56.5)	2/23 (8.7)	4/23 (17.4)	4/23 (17.4)	6/23 (26.1)	32.5 (17.5-64.8)	13.2 (13.1-14.1)	29.8 (24.4-34.4)	1.3 (1.1-2.55)	21/21 (100.0%) over 550 FEU	22/23 (95.7)
Greinacher, 2021 (Greinacher et al., 2021)	Germany and Austria	11	36 (22-49)[b]	9/11 (81.8)	9/11 (81.8)	2/11 (18.2)	1/11 (9.1)	3/11 (27.3)	3/11 (27.3)	19.5[e] (13.0-52.3)	INR 1.34[e] (1.19-1.53)	45[e] (35.3-46.4)	1.3[e] (0.79-2.0)	13mg/L[e] (2.6-21)	9/9 (100.0)
Schultz, 2021 (Schultz et al., 2021)	Norway	5	39 (36-42)	4/5 (80.0)	4/5 (80.0)	-	4/5 (80.0)	1/5 (20.0)	-	19[e] (14-22)	INR 1.1[e] (1.1-1.2)	25[e] (25-29)	1.2[e] (1.2-2.1)	4/5 (80.0) over 35mg/L	5/5 (100.0)
Pavord, 2021 (Pavord et al., 2021)	UK	220	48 (38-56)	119/217 (54.8)	110/220 (50.0)	-	42/220 (19.1)	41/220 (18.6)	63/220 (28.6)	47 (28-76)	13 (10-14)	29 (22-30)	2.2 (1.2-3.1)	24000 FEU (8000-37000)	198/220 (90.0)
Sánchez van Kammen, 2021 (Sánchez van Kammen et al., 2021)	International registry	78	45±14[c]	63/78 (80.8)	78/78 (100.0)	16/70 (22.9)				45 (25-71)					63/69 (91.3)

Anti-PF4 Ab, anti-platelet factor 4 antiboty; aPTT, Activated partial thromboplastin time; CVT, cerebral venous thrombosis; PE, pulmonary thromboembolism; ICH, intracranial haemorrhage; INR, International Normalized Ratio; PT, prothrombin time; SVT, splanchnic venous thrombosis; VITT, vaccine-induced immune thrombotic thrombocytopenia.

[a] The normal ranges for selective variables are as follows: Plt 150-400 cells × 10^9/L, PT 10.0-12.0 sec, aPTT 25.0-37.0 sec, Fibrinogen 1.5-4.0 g/L, D-dimer 0-550 FEU or <0.5 mg/L.

[b] Range not interquartile range.

[c] Mean±standard deviation..

[d] Proportion of ICH among CVT patients.

[e] The highest (D-dimer, aPTT, PT or INR) or lowest (Fibrinogen, platelet) value.

[f] Total anti-PF4 antibody-positive cases; no information on the number of patients tested for these antibodies.

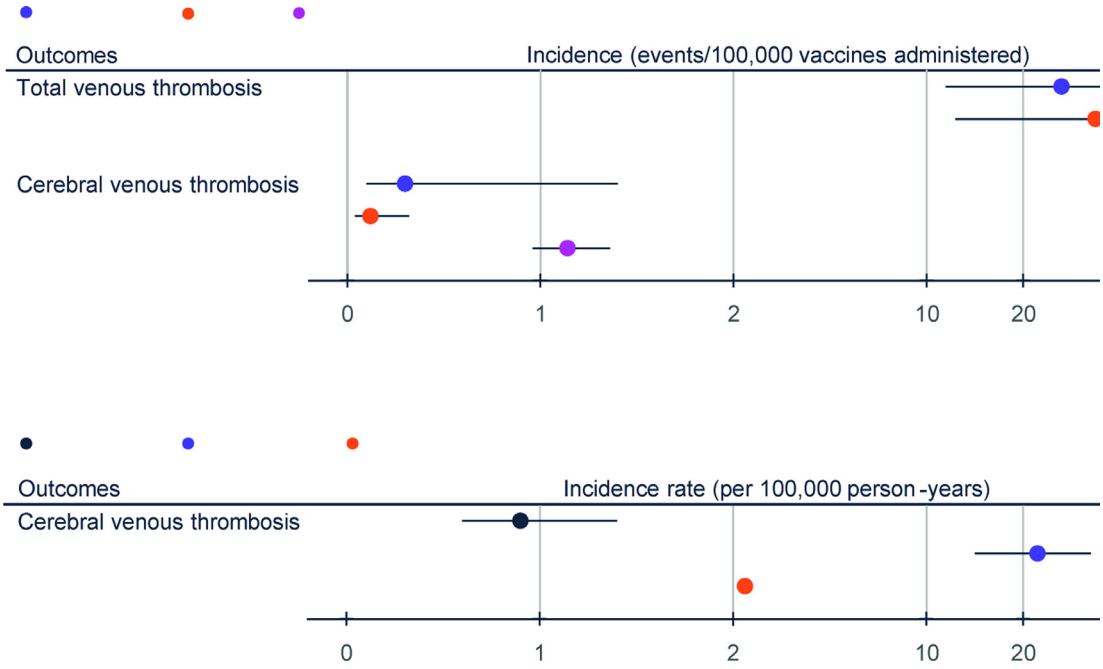

Figure 1. The pooled incidence of venous thrombosis after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination.

Figure 1 (Supplementary Figure S2[a-d]). The incidence of venous thrombosis after the first dose of ChAdOx1 nCoV-19 was 28 (95% CI 12-52) per 100,000 doses administered. The incidences of CVT after ChAdOx1 nCoV-19 and Ad26.COV2.S were 0.3 (95% CI 0.1-1.4) and 1.14 (95% CI 0.96-1.36) per 100,000 administered doses, respectively. Moreover, the CVT incidence rate after ChAdOx1 nCoV-19 vaccination seemed to be higher than that observed in the general population on the basis of pre-pandemic period data.

Ten studies investigated the clinical manifestations and treatment outcomes of VITT after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination (Table 1 and 2). Among them, 5 studies investigated the overall thrombosis in different sites. Given that most VITT cases were identified through its unique infiltration of the cerebral venous system, 5 studies particularly assessed CVT and its clinical outcomes.

The results of the meta-analyses of clinical variables are outlined in Table 3. Regarding demographic variables, the mean age of all patients with VITT was 45.6 years (95% CI 43.8–47.4, k=8, n=599, I^2=57%, p=0.02), and the percentage of females was 65% by overall estimation and 70% (95% CI 57–80, I^2=82%) by meta-analysis. Venous thrombosis risk factors, such as cancer, use of oral contraceptives, infection, recent surgery, or thrombophilia, were present in 20% of patients by overall estimation and 27% by meta-analysis, and headaches were noted in 90% of patients by overall estimation and in 89% by meta-analysis (Supplementary Figure S3[a-h]).

Among all patients with VITT, CVT occurred in 52% by overall estimation and 54% (95% CI 43–65, I^2=42%) by meta-analysis (Figure 2), and intracranial haemorrhage (ICH) occurred in 20% both by overall estimation and meta-analysis (Supplementary Figure S4[c]). The pooled rates of patients with deep vein thrombosis or pulmonary thromboembolism, splanchnic vein thrombosis, and aorto-limb arterial thrombosis were 36%, 19%, and 11%, respectively (Supplementary Figure S4[d,e]).

Regarding all patients with CVT, the rate of accompanying ICH was 48% by overall estimation and 47% by meta-analysis. The rate of extracranial thrombosis was 25% by overall estimation and 33% by meta-analysis, and the pooled proportions of pulmonary thromboembolism, splanchnic vein thrombosis, and aorto-limb arterial thrombosis in patients with CVT were 16%, 13%, and 6%, respectively (Supplementary Figure S4[g-n]).

Supplementary Table S5 describes the pooled-mean laboratory values of all patients with VITT. The pooled-mean initial and nadir platelet counts were very low (50.0×10^9/L and 33.2×10^9/L, respectively) and the prothrombin time was prolonged (13.4 s). The nadir fibrinogen and peak D-dimer levels were 1.6 g/L and 26.3 mg/L, respectively. Of note, the anti-PF4 antibody test was conducted in 7 studies, and the positivity rate was 91% (95% CI 88–94, I^2=0%) in the meta-analysis (Figure 3).

Non-heparin anticoagulation was administered in 64% of patients by overall estimation and in 65% (95% CI 45-73, I^2=77%) by meta-analysis, whereas 35% (95% CI 23-48, I^2=68%) of patients received heparin-based anticoagulation. The pooled proportions of patients treated with intravenous immunoglobulin (IVIG), corticosteroids, platelet transfusion, and intervention were 69%, 44%, 25%, and 30%, respectively (Supplementary Figure S4[o-u]). Notably, the mortality rate was 30% by overall estimation and 32% (95% CI 24-41, I^2=69%) by meta-analysis (Figure 4). There was no significant difference in mortality rate between heparin- and non-heparin-based anticoagulation (risk ratio 0.84, 95% CI 0.47-1.50, I^2=0%, p=0.80; Figure 5) according to the meta-analysis of 3 studies that had available data (Pavord et al., 2021; Perry et al., 2021; Tiede et al., 2021). Supplementary Figure S5 demonstrates the publication bias of these 3 studies.

Discussion

As the vaccine rollout expands worldwide, more precise information about vaccine safety has become essential. Owing to the lack of a comprehensive understanding of VITT after ChAdOx1-nCoV or Ad26.COV2.S vaccination, we conducted a systematic analysis of published retrospective cohort studies and case series to investigate the clinical features and outcomes of VITT. To our knowledge, this study was the first attempt to meta-analyse recently reported studies from clinical manifestations to treatment outcomes. Therefore, this meta-analysis will provide a more systematic understanding of the current patterns of diagnosis, treatment, and prognosis of adenoviral vector vaccine-related thrombosis.

Table 2
Treatment modalities and outcomes of patients with vaccine-induced immune thrombotic thrombocytopenia (VITT) after ChAdOx1 nCov-19 or Ad26.COV2.S vaccination

Author	Month of report	Treatment modalities							Outcome		
		IVIG	Steroid	Heparin AC	Non-heparin AC	Platelet transfusion	Plasma exchange	Intervention	Overall mortality	Mortality among non-heparin AC	Mortality among heparin AC
Perry (Perry et al., 2021)	August 2021	55/70 (78.6)	51/70 (72.9)	16/70 (22.9)	Parenteral : 50/70 (71.4); DOAC: 22/70 (31.4)	25/70 (35.7)	16/70 (22.9)	Endovascular: 9/70 (12.9) ; Surgery: 13/70(18.6)	20/70 (28.6)	9/50 (18.0)	3/16 (18.8)
Tiede (Tiede et al., 2021)	July 2021	3/5 (60.0)	-	1/5 (20.0)	Argatroban: 4/5 (80.0)	-	-	-	0/3 (0.0)	0/2 (0.0)	0/1 (0.0)
Krzywicka (Krzywicka et al., 2021)	July 2021	-	-	-	-	-	-	-	44/117 (37.6)	-	-
Schulz (Schulz et al., 2021)	July 2021	-	-	-	-	-	-	-	9/53 (17.0)	-	-
See (See et al., 2021)	April 2021	7/12 (58.3)	3/12 (25.0)	6/12 (50.0)	All types: 4/12 (33.3)[a]; Argatroban : 2/12 (16.7)	4/12 (33.3)	-	-	3/12 (25.0)	-	-
Scully (Scully et al., 2021)	June 2021	-	-	-	-	–	-	-	7/23 (30.4)	-	-
Greinacher (Greinacher et al., 2021)	June 2021	-	-	5/9 (55.6)	-	-	-	-	6/11(54.5)	-	2/5 (40.0)
Schultz (Schultz et al., 2021)	April 2021	4/5 (80.0)	4/5 (80.0)	5/5 (100.0)	-	-	-	-	3/5 (60.0)	-	-
Pavord (Pavord et al., 2021)	August 2021	158/220 (71.8)	58/220 (26.4)	50/220 (22.7)	150/220 (68.2)	30/220 (13.6)	17/220 (7.7)	32/220 (14.5)[b]	49/220 (22.3)	24/149 (16.1)	10/50 (20.0)
Sánchez van Kammen, 2021 (Sánchez van Kammen et al., 2021)	September 2021	47/78 (60.3)	25/78 (32.1)	30/78 (38.5)	37/78 (47.4)	20/78 (25.6)	6/78 (7.7)	Endovascular : 16/77 (20.8); Surgery: 23/77(29.9)	36/76 (47.4)		12/29 (41.4)

Data are n(%) or n/N (%).
AC, anti-coagulation; IVIG, intravenous immunoglobulin; DOAC, direct oral anticoagulant; VITT, vaccine-induced immune thrombotic thrombocytopenia.
[a] During whole period of hospitalisation, 6 additional patients shifted to non-heparin anti-coagulation (10/12 [83.3%]).[b]Including patients who received decompressive craniectomy or endovascular treatments.

Table 3
Meta-analyses of the clinical characteristics and outcomes of vaccine-induced immune thrombotic thrombocytopenia

Variables	Number of studies	Total number of patients	Number of events	Proportion (overall)	Proportion by meta-Analysis (95% CI)		Heterogeneity I^2 (p-value)	τ^2
					Random effect	Fixed effect		
Demographic								
Female	9	605	395	65%	70% (57-80)	64% (59-67)	82% (p <0.01)	0.436
Age under 50	7	346	209	60%	60% (53-67)	59% (53-64)	52% (p=0.05)	0.024
Medical history	6	285	134	47%	37% (22-56)	49% (43-55)	80% (p<0.01)	0.698
Venous risk factor[a]	4	347	70	20%	27% (13-49)	22% (18-27)	89% (p<0.01)	0.812
Hormone therapy	6	347	33	10%	10% (5-21)	12% (8-16)	71% (p<0.01)	0.673
Symptom - headache	5	170	153	90%	89% (78-95)	88% (82-92)	33% (p=0.20)	0.316
VITT								
CVT	5	264	137	52%	54% (43-65)	52% (45-58)	42% (p=0.14)	0.067
DVT or PE	3	254	92	36%	36% (31-42)	36% (31-42)	0% (p=0.67)	0.00
ICH	5	264	52	20%	20% (15-25)	20% (15-25)	44% (p=0.13)	<0.0001
SVT	5	264	50	19%	19% (15-24)	19% (15-24)	0% (p=0.97)	0.00
PVT	3	248	34	14%	14% (10-19)	14% (10-19)	0% (p=0.92)	0.00
CVA	3	248	21	8%	12% (4-29)	9% (6-13)	58% (p=0.09)	0.570
ALT	2	243	27	11%	11% (7-18)	11% (8-16)	7% (p=0.30)	0.040
CVT								
ICH with CVT	4	213	103	48%	47% (28-68)	48% (41-55)	86% (p<0.01)	0.554
CVA with CVT	2	83	2	2.4%	3% (1-10)	3% (1-10)	0% (p=0.89)	0.00
All Extracranial thrombosis	6	361	92	25%	33% (18-52)	29% (24-34)	88% (p<0.01)	0.784
DVT in CVT	5	352	19	5%	7% (3-17)	7% (5-11)	66% (p=0.02)	0.699
PE in CVT	6	361	46	13%	16% (9-27)	16% (12-20)	74% (p<0.01)	0.450
SVT in CVT	5	291	28	10%	13% (7-24)	11% (8-15)	60% (p=0.04)	0.365
PVT in CVT	3	95	16	17%	17% (11-26)	17% (11-26)	0% (p=0.65)	0.00
ALT in CVT	3	92	5	5%	6% (3-13)	6% (3-13)	0% (p=0.76)	0.00
Laboratory findings[a]								
Anti-PF4 Ab (+)	7	395	364	92%	91% (88-94)	91% (88-94)	0% (p=0.77)	0.00
Treatment								
Heparin	7	399	113	28%	35% (23-48)	28% (24-33)	68% (p<0.01)	0.283
Non-heparin	5	245	385	64%	60% (45-73)	63% (58-68)	77% (p<0.01)	0.303
IVIG	6	390	274	70%	69% (61-77)	70% (65-74)	33% (p=0.19)	0.081
PEx	3	368	39	11%	11% (5-23)	12% (9-16)	84% (p<0.01)	0.456
Corticosteroid	5	385	141	37%	44% (23-67)	36% (31-41)	91% (p<0.01)	0.951
Plt transfusion	4	380	79	21%	25% (15-38)	22% (18-27)	83% (p<0.01)	0.295
Intervention	3	367	93	25%	30% (13-54)	28% (23-33)	95% (p<0.01)	0.774
Outcome								
Overall mortality	10	590	177	30%	32% (24-41)	31% (27-35)	69% (p<0.01)	0.206
Heparin	5	101	27	27%	28% (17-42)	28% (20-38)	21% (p=0.28)	0.170
Non-heparin	3	201	33	16%	17% (12-22)	17% (12-22)	0% (p=0.95)	0.00

Data are n (%) or n/N (%)
Anti-PF4 Ab, anti-platelet factor 4 antibody; ALT, aorto-limb arterial thrombosis; CVA, cerebrovascular attack; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ICH, intracranial haemorrhage; IVIG, intravenous immunoglobulin; MI, myocardial infarction; PE, pulmonary thromboembolism; PEx, plasma exchange; Plt, platelet; PVT, portal vein thrombosis; SVT, splanchnic vein thrombosis; VITT, vaccine-induced immune thrombotic thrombocytopenia.
[a] Additional laboratory findings with continuous variables are delineated in Table 4.

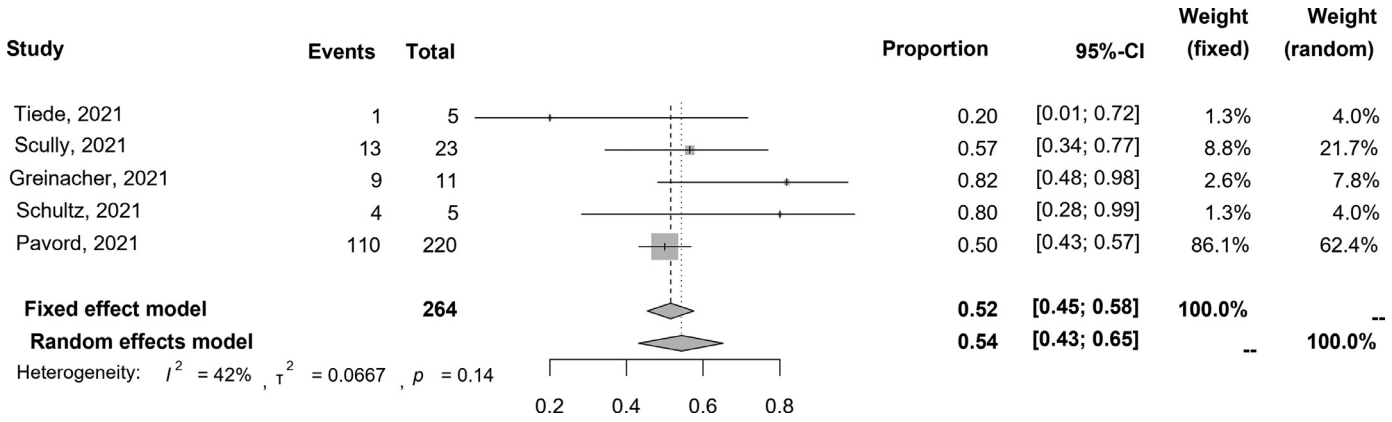

Figure 2. Forest plot of meta-analysis to estimate the proportion of cerebral venous thrombosis in all patients with vaccine-induced immune thrombotic thrombocytopenia.

Although most studies used similar criteria to diagnose VITT, there was also significant variability among them. Recently published studies (Pavord et al., 2021; Perry et al., 2021) used objective measures excluding specialists' opinion in diagnosis. However, whether all 5 criteria (recent vaccination, thrombosis, thrombocytopenia, elevated D-dimer levels, and anti-PF4 antibody positivity) should be met for VITT diagnosis still needs to be addressed. Adopting a strict cut-off for thrombocytopenia (150×10^9/L), for instance, could exclude patients with sufficient evidence of VITT in manifestations and other criteria (Perry et al., 2021). Studies published between April and July used clinical opinions of specialists in neurology or haematology as one of the inclusion cri-

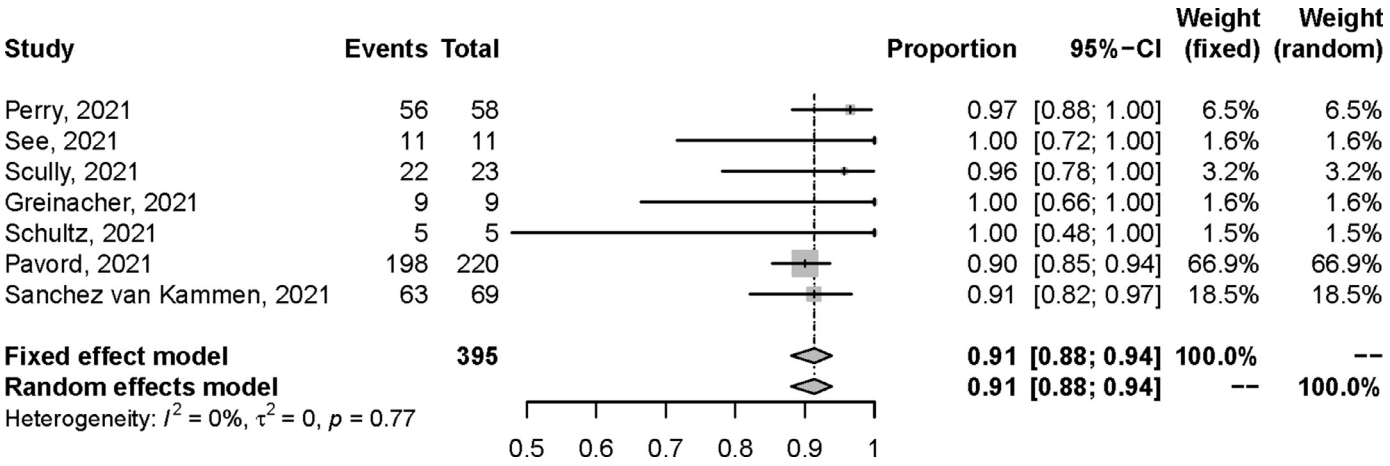

Figure 3. Forest plot of meta-analysis to estimate the proportion of patients with positive antiplatelet factor 4 antibody test.

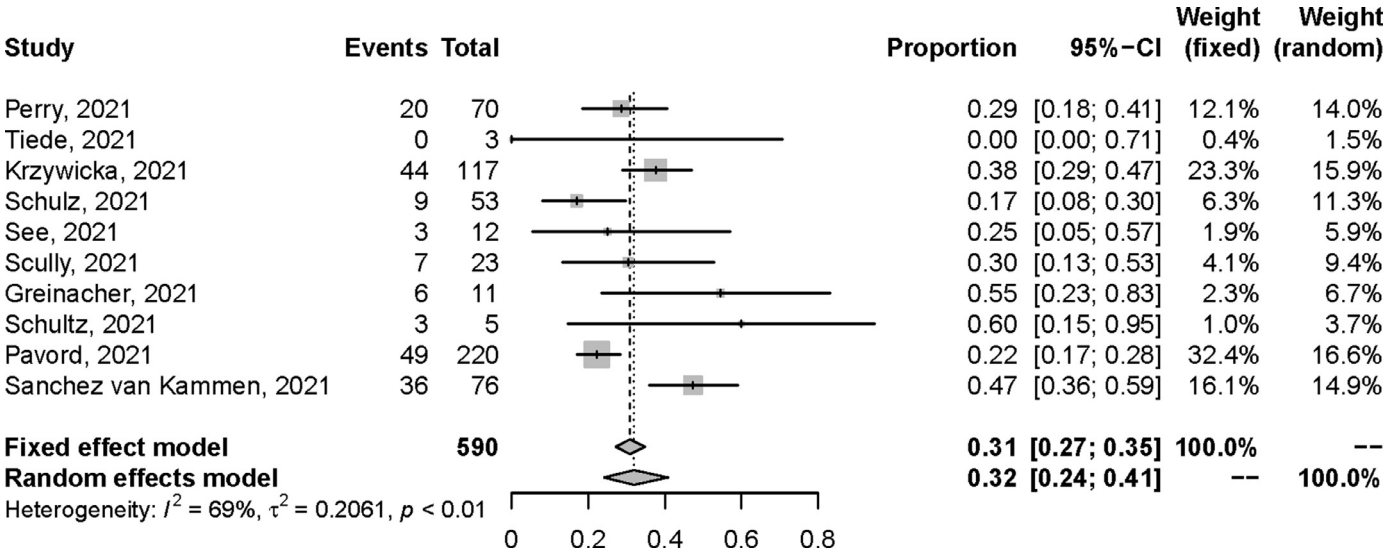

Figure 4. Forest plot of meta-analysis to estimate the overall mortality rate of patients with vaccine-induced immune thrombotic thrombocytopenia.

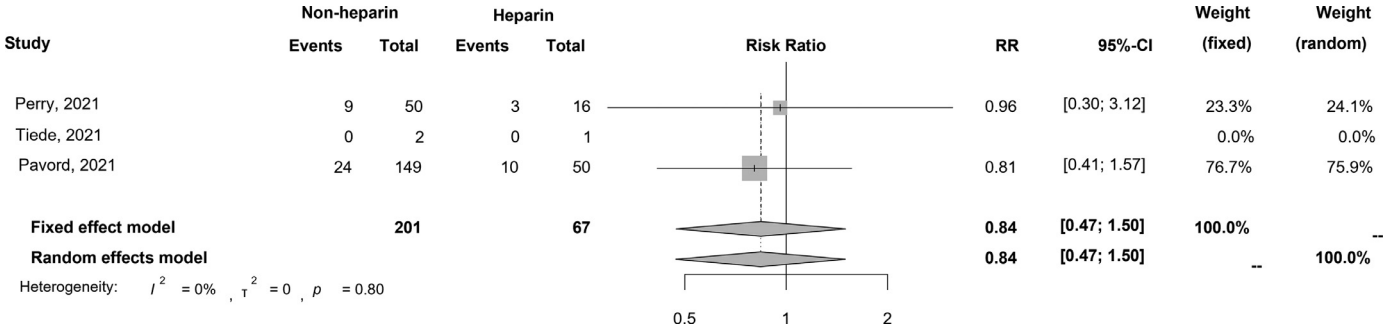

Figure 5. Forest plot of meta-analysis to compare the mortality rate between the 2 types of anticoagulation treatments.

teria (Greinacher et al., 2021b; Krzywicka et al., 2021; Sánchez van Kammen et al., 2021a; Schultz et al., 2021; Schulz et al., 2021; Scully et al., 2021; See et al., 2021; Tiede et al., 2021). Subsequently, this could introduce biases with regard to the local level of SARS-CoV-2 infection, clinical environments, or available tests among those specialists. A more precise and uniformly constructed consensus on VITT diagnosis must be established via a higher-level collaboration of experts.

As noted in this study, VITT occurred more commonly in females, and more than half of patients were under the age of 50. After it was found that young female individuals were vulnerable to VITT from early reports, many countries modified their eligibility criteria for adenoviral vector vaccines. However, as recent studies described (Pavord et al., 2021; Perry et al., 2021), male and older people are not spared from VITT. Although some patients had risk factors related to venous thrombosis, VITT occurred even in people without these predispositions, as previously reported (Idiculla et al., 2020; Marjot et al., 2011). Therefore, regardless of patients' pre-existing risk factors for thrombosis, clinicians should consider the possibility of diagnosing VITT

in patients with suspected thrombosis after SARS-CoV-2 vaccinations.

When CVT was first reported after vaccination, it was uncertain whether cases of this rare disease were indeed an adverse event of vaccination or coincidental. All other types of thrombosis after vaccination were also reviewed by experts. In the attempts to understand this disease, the connection between VITT and anti-PF4 positivity was used to differentiate this rare phenomenon (Greinacher et al., 2021). Later, it was suggested that inter-reactivity between the adenoviral vaccine and platelets or PF4 could be related to the pathogenesis of VITT. The free nucleic acid in the vaccines could adhere to PF4 and trigger the formation of PF4-reactive autoantibodies, resulting in VITT (Greinacher et al., 2021b; Jaax et al., 2013). Although many experts suggest that there would be a similar process between VITT and HIT (Cines and Bussel, 2021; Vayne et al., 2021), VITT appears to cause more frequent thrombotic events in the cerebral venous system than HIT. In addition, although VITT and HIT are anti-PF4 disorders, they had different binding amino acids in PF4 according to alanine-scanning mutagenesis, and VITT anti-PF4 antibodies had a more robust binding response to PF4 and PF4-heparin complexes than HIT anti-PF4 antibodies (Huynh et al., 2021). The high frequency of CVT in VITT was comparable with the clinical phenomenon of medical spontaneous HIT syndrome, which occurs in post-infection scenarios or where no proximate illness or surgery is identified (Warkentin et al., 2021). Thus, the connection between VITT and CVT might be related to the difference in binding site on PF4 compared with HIT. Moreover, the molecular mimicry between the vaccine-induced proteins of SARS-CoV-2 and human components might increase the risk of adverse effects by leading to the production of pathological autoantibodies, resulting in vaccine-induced autoimmunity (Dotan and Shoenfeld, 2021; Segal and Shoenfeld, 2018). Furthermore, the reason why these thrombotic events occur frequently as CVT or splanchnic vein thrombosis remains uncertain, and further studies are warranted. However, because these are unusual locations for thrombosis, clinicians suspected VITT when patients with recent SARS-CoV-2 vaccination history presented with these thrombotic patterns (CVT or splanchnic vein thrombosis) (Ciccone, 2021).

The introduction of an anti-PF4 antibody test to diagnose this rare disease was first described in Germany (Greinacher et al., 2021). Although patients were not previously exposed to heparin, they exhibited a pattern of clinical manifestations similar to that of HIT. Later, the anti-PF4 antibody test was frequently used in other studies (Pavord et al., 2021; Perry et al., 2021; Sánchez van Kammen et al., 2021a; Scully et al., 2021; See et al., 2021; Schultz et al., 2021), and our meta-analysis revealed a high positivity rate (91%). In the patients with CVT before the COVID-19 pandemic, the anti-PF4 positivity rate was extremely low compared with patients with VITT-related CVT (Sánchez van Kammen et al., 2021b). The cut-off value of optical density in the test, which was measured to display the positivity, has not been determined, but it seems to have a higher value in patients with VITT than in the normal population (Hursting et al., 2010; Schultz et al., 2021). This pooled effect could be less informative because of a high proportion of single studies (Pavord et al., 2021); further analysis of this value would be warranted.

The consensus on VITT treatment has evolved throughout the pandemic compared with the early period when different modalities were introduced to manage this rare adverse event. In our meta-analysis, there was no significant difference in mortality between heparin-based and non-heparin-based anticoagulation strategies. However, only 3 studies were included in the meta-analysis because of data availability issues; thus, the result should be interpreted with caution, and there was a trend of lower mortality in the non-heparin group. As more VITT cases are reported, this trend will be clearer and further analyses would be needed to confirm the benefit of non-heparin-based anticoagulants. Immunoglobulins were also widely used (73%) to manage VITT, although there were no available data comparing the use and non-use of IVIG. Given that the current expert consensus recommends the administration of IVIG and non-heparin anticoagulation for initial management (Cines and Bussel, 2021; Makris et al., 2021; Perry et al., 2021), clinicians should be cautious in interpreting the results of this study considering the shift in clinical practices during the pandemic.

The overall mortality of patients with VITT was 29% in the meta-analysis, suggesting a high fatality rate. Given that most VITT cases were identified because of their involvement in the cerebral venous system, which frequently led to a fatal outcome, this rate could be overestimated because it does not take into account all sites of thrombosis, including extracranial involvement. A subanalysis of extracranial involvement according to the pattern of each thrombosis seems necessary.

The incidence of CVT appeared to be higher in ChAdOx1 nCoV-19 recipients than in the pre-pandemic general population. This result follows previous reports of high thromboembolism and CVT after ChAdOx1 nCoV-19 vaccine administration in several European countries (Hippisley-Cox et al., 2021; Simpson et al., 2021). However, the incidence in South Korea (Huh et al., 2021) seems to be lower than that observed in other reports from European countries. This could be related to the protective genetic traits against venous thromboembolism in Asians (Klatsky et al., 2000). However, because of insufficient data from other Asian countries, it is premature to describe this tendency. As the vaccine rollout expands in Asia and Africa, further analysis of incidence by geographical and demographical difference would be necessary. Furthermore, even though adenoviral vector-based vaccines carry a risk of VITT, clinicians and the public should acknowledge the much greater thromboembolism risk after contracting SARS-CoV-2 (Terpos et al., 2020).

There are several limitations to this study. First, the included studies had some degree of discrepancy in defining VITT, although thrombosis and thrombocytopenia were commonly mentioned. Because this was a rare adverse event after vaccinations, early case series had heterogenic characteristics of included patients. Additionally, 2 studies from database analysis did not have enough clinical information in terms of patient severity. These issues could have led to an overestimation of the mortality rate and might pose a risk of bias in generalizing the results to the public. Therefore, additional clinical trials or multicentre studies based on the current definition of VITT should be performed to address clinical outcomes in VITT. Second, despite our comprehensive approach, there is limited evidence for generalization because the included studies were retrospectively designed. Although mortality rates and laboratory variables were presented after incorporation, these should be cautiously interpreted because study diversity was not sufficiently assessed in this process. Because of variability in the inclusion criteria, under or over-reporting of cases could have also biased our results. Third, the heterogeneity among outcomes was substantial, and cautious interpretation is necessary according to different clinical settings. This heterogeneity may be caused by differences between studies in design, disease severity, age distribution, local policy of vaccination, or other unidentified variables. Additionally, there is a possibility of double-counted cases among included studies. We could not match everyone's data because of the lack of medical records for all patients, which could have led to overestimation relative to real-world clinical data.

Conclusion

This is the first systematic review to analyse VITT incidence after adenovirus-based vaccination and to evaluate the manifes-

tations, treatments, and outcomes of this rare adverse event. This unusual thrombosis occurred in various sites, with cases of CVT (54%), deep vein thrombosis or pulmonary thromboembolism (36%), and splanchnic vein thrombosis (19%), and the anti-PF4 test was positive in 91% of cases. Considering the relatively high mortality of VITT, early recognition based on current clinical evidence is essential to improve its clinical outcomes.

Conflict of Interest

The authors disclose no financial or non-financial conflicts of interest, including funding, provision of study materials, medical writing, and article processing charges.

Ethical Approval statement

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Authors' contributions

Ah Young Kim: Conceptualization, Methodology, Data Curation, Formal analysis, Resources, Investigation, Writing - Original Draft, Writing – Review & Editing. **Wongi Woo:** Conceptualization, Methodology, Data Curation, Formal analysis, Investigation, Software, Writing - Original Draft, Writing – Review & Editing. **Dong Keon Yon:** Methodology, Data Curation, Formal analysis, Resources, Investigation, Writing - Original Draft, Writing – Review & Editing. **Seung Won Lee:** Methodology, Data Curation, Formal analysis, Resources, Investigation, Writing - Original Draft, Writing – Review & Editing. **Jae Won Yang:** Resources, Writing – Review & Editing. **Ji Hong Kim**: Resources, Writing – Review & Editing. **Seoyeon Park:** Software, Visualization, Writing – Review & Editing. **Ai Koyanagi:** Writing – Review & Editing. **Min Seo Kim:** Writing – Review & Editing. **Sungsoo Lee:** Writing – Review & Editing. **Jae Il Shin:** Conceptualization, Methodology, Validation, Supervision, Project administration Writing – Review & Editing. **Smith Lee:** Writing – Review & Editing.

Data Availability Statement

The data underlying this article will be shared by the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.03.034.

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